6.3.83

Cuk-102946-7-P024815

HIGH-VOLTAGE ELECTRON MICROSCOPIC STUDY OF THE INNER EAR

TECHNIQUE AND PRELIMINARY RESULTS

TOMONORI TAKASAKA, MD

HIDEICH SHINKAWA, MD

SHO HASHIMOTO, MD

KOZO WATANUKI, MD

KAZUTOMO KAWAMOTO, MD

⑦

Supplement 101 — Vol. 92, January-February 1983, No. 1, Part 2

ANNALS OF OTOLOGY, RHINOLOGY & LARYNGOLOGY
ANNALS OF HEAD & NECK MEDICINE & SURGERY

HIGH-VOLTAGE ELECTRON MICROSCOPIC STUDY OF THE INNER EAR

TECHNIQUE AND PRELIMINARY RESULTS

Tomonori Takasaka, MD
Hideich Shinkawa, MD
Sho Hashimoto, MD
Kozo Watanuki, MD
Kazutomo Kawamoto, MD

HIGH-VOLTAGE ELECTRON MICROSCOPIC STUDY OF THE INNER EAR

TECHNIQUE AND PRELIMINARY RESULTS

TOMONORI TAKASAKA, MD
HIDEICH SHINKAWA, MD
SHO HASHIMOTO, MD
KOZO WATANUKI, MD
KAZUTOMO KAWAMOTO, MD

SENDAI, JAPAN

The technique and some preliminary results of the application of high-voltage electron microscopy (HVEM) to the study of inner ear morphology in the guinea pig are reported in this paper. The main advantage of HVEM is that sharp images of thicker specimens can be obtained because of the greater penetrating power of high energy electrons. The optimum thickness of the sections examined with an accelerating voltage of 1,000 kV was found to be between 500 to 800 nm. The sections below 500 nm in thickness often had insufficient contrast, while those above 800 nm were rather difficult to interpret due to overlap of images of the organelles. The whole structure of the sensory hairs from the tip to the rootlet was more frequently observed in the 800-nm thick sections. Thus the fine details of the hair attachment to the tectorial membrane as well as the hair rootlet extension into the cuticular plate could be thoroughly studied in the HVEM. In specimens fixed in aldehyde containing 2% tannic acid, the attachment of the tips of the outer hair cell stereocilia to the tectorial membrane was observed. For the inner hair cells, however, the tips of the hairs were separated from the undersurface of the tectorial membrane. The majority of the rootlets of the outer hair cells terminated at the midportion of the cuticular plate, while most of the inner hair cell rootlets traversed the entire width of the cuticular plate and extended into the apical cytoplasm. These differences in ultrastructural appearance may indicate that the two kinds of hair cells play different roles in the acoustic transduction process. The three-dimensional arrangement of the nerve endings on the hair cells was also studied by the serial thick-sectioning technique in the HVEM. In general, an entire arrangement of the nerve endings was almost completely cut in less than ten 800-nm thick sections instead of the 50- to 100-ultrathin (ie, less than 100 nm) conventional sections for transmission electron microscopy. The present study confirms an earlier report that the first row outer hair cells in the third cochlear turn are innervated by nearly equal numbers of efferent and afferent endings, the average number being nine.

Applications of the high-voltage electron microscope (HVEM) to biological specimens were said to have finally entered a new era with the review made by Glauert[1] in 1974. However, considering that the institutions utilizing HVEM are limited and the majority of the work involving HVEM involves nonbiological materials, it is hardly true to say that such application is being sufficiently promoted even today. On the other hand, 200-kV class HVEMs are increasingly seen these days and the time seems to have come for us to ascertain whether or not the application of HVEM can be further expanded. The authors have had the opportunity to use the JEM-1000 at the Million-Volts Electron Microscope Laboratory of Tohoku University since 1975 and have been conducting basic studies[2-7] on the application of the HVEM to the inner ear morphology. The purpose of this paper is to report the technical details for the HVEM application to inner ear investigation and to present some preliminary results on the sensory hairs in the guinea pig cochlea as well as on the arrangement of the efferent and afferent nerve endings on the outer hair cells (OHC).

MATERIALS AND METHODS

Specimens from ten albino guinea pigs (250-350 g) were studied by the HVEM (JEM-1000, Tohoku Univ.). The guinea pigs were anesthetized with an intraperitoneal injection of Nembutal (30 mg/kg), and the temporal bullae were opened under a dissecting microscope. Perfusion of the perilymphatic spaces were performed using handmade glass pipettes from the microhole made at the lateral wall of the scala tympani to the second hole at the scala vestibuli of the basal turn.

The following fixatives were used: 1) 2.5% glutaraldehyde (Taab), 2% tannic acid, 1% sodium sulfate, 1% dimethyl sulfoxide and .07 M veronal-acetate buffer (pH 6.8),[8] and 2) 2.5% glutaraldehyde (Taab) and 0.1 M phosphate buffer (pH 7.4).

After perfusion, the guinea pigs were immediately decapitated and the cochleas were dissected from the skull and immersed in toto into the same fixative for several hours. The excess bone of the temporal bulla and apical part of the cochlear bony wall were carefully removed in the fixative under the dissecting microscope. The cochleas were thoroughly rinsed overnight in the buffer solution containing 6% sucrose at room temperature before postfixing with 1% OsO_4 in the buffer solution. After osmification for one hour, the specimens were washed in distilled water and subjected to an hour of block-staining in a 4% aqueous solution of uranyl acetate. The cochleas were dehydrated in an ascending series of ethanol followed by propylene oxide and embedded in epoxy resin (Epon 812 9 cc, NMA 5 cc, DDSA 5.5 cc and DMP-30 0.14 cc). The Sorvall MT-5000 Ultratome was used for sectioning so that sections with thicknesses between 5 and 995 nm could be obtained. Serial thick sections (500-800 nm) were picked up on single-hole grids coated with Formvar and stained with aqueous solutions of uranyl acetate (15 minutes) and lead citrate (5 minutes) at room temperature. The specimens were observed in the JEM-1000 HVEM with the accelerating voltage of 1,000 kV.

From the Department of Otolaryngology, Tohoku University School of Medicine, Sendai, Japan.

Presented at the Fourth Midwinter Research Meeting of the Association for Research in Otolaryngology, St. Petersburg Beach, Florida, January 19-21, 1981.

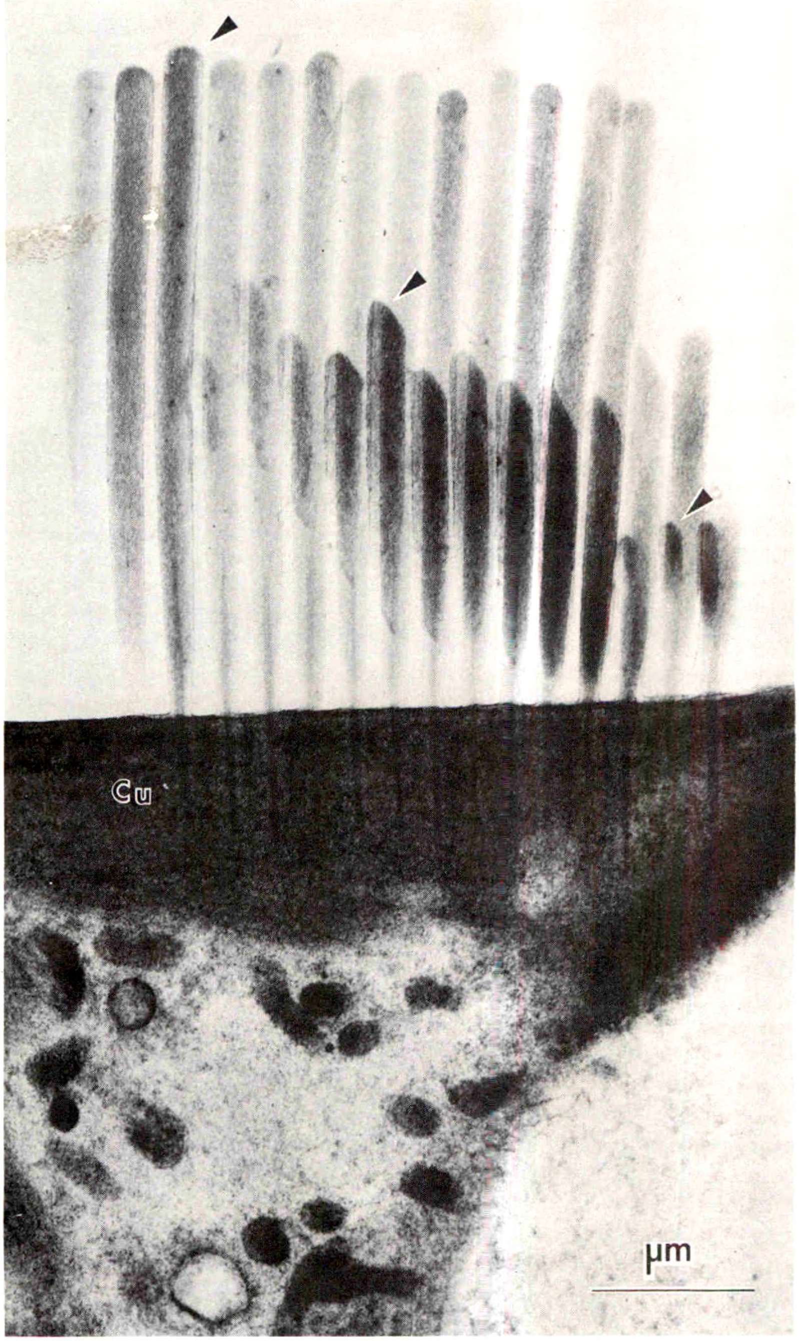


Fig. 1. High-voltage electron micrograph showing apical portion of guinea pig OHC. Three rows (arrows) of hair bundle are clearly seen. Due to thickness of section (800 nm), longest hairs (left arrow) are completely visible from their tops to basal rootlets embedded in cuticular plate (Cu).

RESULTS

The optimum thickness of the sections examined with an accelerating voltage of 1,000 kV was found to be between 500 to 800 nm. The sections below 500 nm in thickness showed relatively poor image contrast which often makes focusing more difficult. In the thick sections above 800 nm, the cell organelles and fine membranous structures were insufficiently defined even with the greater penetrating power of the 1,000 kV electron beam.

Fine Structure of the Sensory Hairs. In Figure 1, the whole structure of the 11 longest hairs from their tips to the basal rootlets is clearly visible. This section is about 800 nm thick and was photographed in the HVEM. With ultrathin sections (60-100 nm), it is quite difficult to obtain the entire sensory hair in the section unless the plane of the section fortuitously coincides with the longitudinal axis of the hairs. The HVEM technique allows examination of the attachment of the sensory hair tips to the tectorial membrane. In the specimens fixed with the fixative containing 2% tannic acid, the tips of the hairs of the OHC were definitely embedded in the tectorial membrane as shown in Figures 2 and 3. The unit membrane of each hair is clearly seen in the thick specimens and the regularly arranged parallel filaments are also visible in the hairs. The diameter of these filaments is about 6.5 nm. The tectorial membrane is also composed of the filamen-

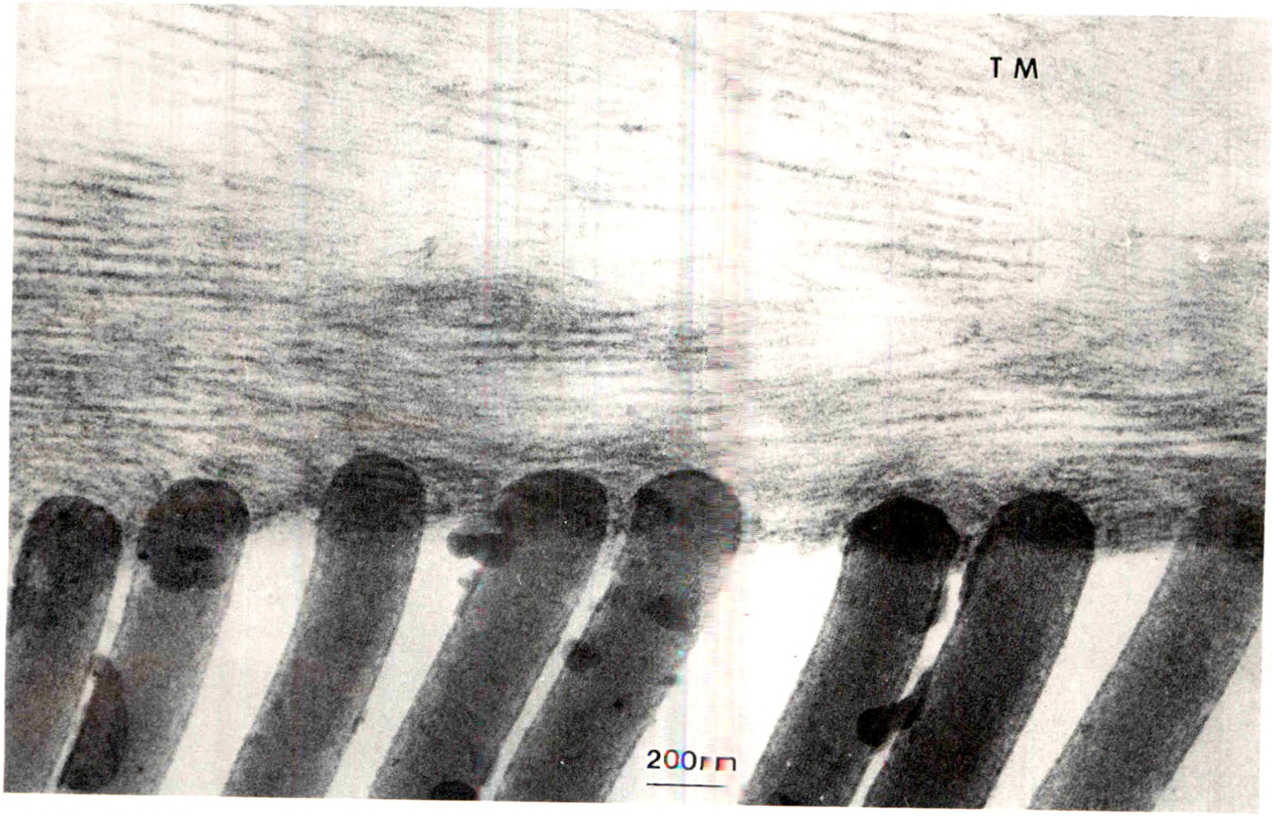


Fig. 2. Attachment of stereocilia of OHC to tectorial membrane (TM). It is clear that TM is composed of fine and coarse filaments, and that both kinds of filaments are directly attached to unit membrane of hairs. Note parallel array of actin filaments in stereocilia.

tous material, but the diameters of these filaments are much larger than those in the hairs. Within the tectorial membrane, fine filaments are seen between the coarse filaments, both attaching directly to unit membrane of the hairs (Figs. 2 and 3). In contrast, the attachment of the inner hair cell (IHC) stereocilia to the tectorial membrane was not definitely observed in the present material. As shown in Figure 4, four of the longest hairs on the IHC are very close to Hensen's stripe, but their tips are not in obvious contact with the undersurface of the tectorial membrane.

Every sensory hair possesses a rootlet which extends into the cuticular plate as an anchor. In the 800-nm thick sections, it was possible to visualize the entire course of the rootlets in the cuticular plate (Figs. 1, 4 and 5). In the OHC, the majority of the rootlets terminate in the midportion of the cuticular plate, whereas in the IHC, almost all rootlets traverse the entire width of the cuticular plate and extend into the apical cytoplasm. The average length of the rootlets is about 700-1,000 nm in the OHC of the third cochlear turn, whereas the length of the IHC rootlets is about 1,500 nm, which includes an additional 500-nm extension in the apical cytoplasm. In other words, the rootlets of the IHC stereocilia are about twice as long as those of the OHC. As is clearly visible in Figures 4 and 5, the rootlets of the IHC often end in the vicinity of the subcuticular mitochondria.

Three-dimensional Reconstruction of the Efferent and Afferent Nerve Endings by Means of Serial Thick Sections. The scale in Figure 6 shows the number of sections which must be cut in order to include the entire arrangement of the nerve endings on an OHC. In the case of 100-nm thin sections, at least 50 serial sections must be cut. However, with 800 nm sections, six or seven sections are sufficient to include all the nerve endings. Therefore, we cut the OHC in the third cochlear turn at a thickness of 800 nm. It has already been shown by conventional transmission electron microscope studies that the afferent nerve endings are small, averaging about 900 nm in diameter and containing a few mitochondria and dispersed vesicles of various sizes. Consequently, the afferent endings may be included in their entirety in one or two serial sections of 800-nm thickness. The six micrographs of Figure 7 show consecutive horizontal sections through the nerve endings on a first row OHC in the third turn of the guinea pig cochlea. Figure 7a shows two large efferent endings (★1 and 2) at the bottom of the cell and one afferent ending (*1) to the right. Figure 7b reveals a new afferent ending (*2) between ★1 and ★2, and *3 (afferent) is also present to the left. The number of the nerve endings has increased in Figure 7c; new efferent endings (★3, 4 and 5) and afferent endings (*4 and 5) are present. A synaptic bar (arrowhead) is clearly visible in hair cell cytoplasm adjacent to afferent ending *4. In Figure 7d, the small amount of hair cell cytoplasm indicates that this section is

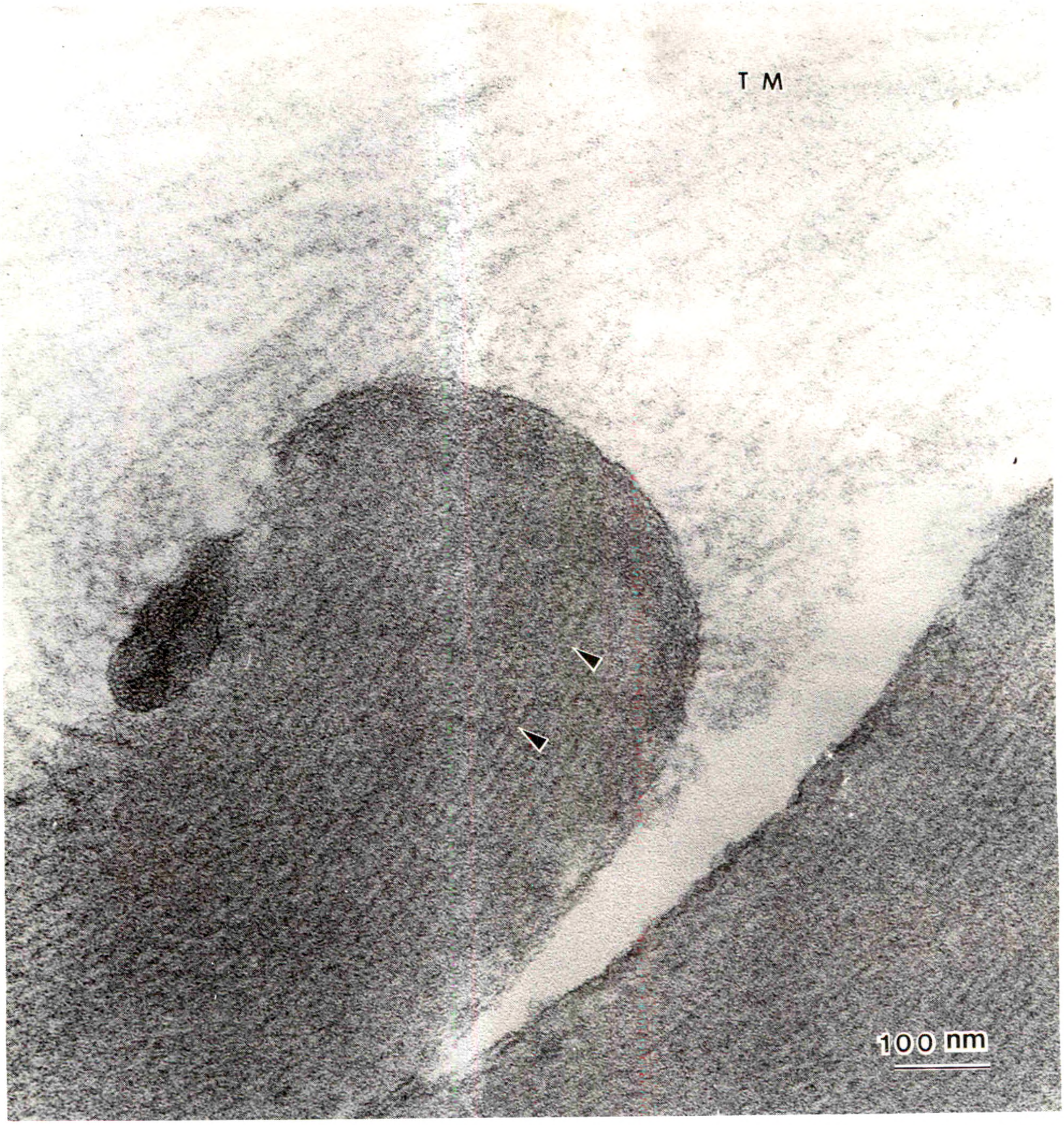


Fig. 3. Higher magnification of attachment of hair tips to tectorial membrane (TM). Two arrows indicate actin filament with diameter of about 6.5 nm.

near the bottom of the hair cell. New efferent endings (★6, 7, 8 and 9) and afferent endings (*6, 7 and 8) are seen. Four synaptic bars (arrowheads) are also present in the cytoplasm. The bars can be seen at a higher magnification in Figure 8. Additional afferent nerve endings (Fig. 7e: *9, 10, 11, 12 and 13) and two other efferent endings (Fig. 7f: ★10 and 11) are seen in the central part of the cluster of the nerve endings. No more hair cell cytoplasm is seen in these micrographs. Since no additional endings were visible in the next section, it was concluded that this cell has 11 efferent endings and 13 afferent endings as well as six synaptic bars within the cytoplasm. The preliminary results of an examination of ten hair cells in which the nerve endings were completely cut by serial thick sections are shown in the Table. The total number of the nerve endings per hair cell varied from 12 to 24, indicating that the cells are not innervated by a fixed number of the nerve endings. The ratio of efferent and afferent nerve endings also varies from one cell to another: in cells 4, 5 and 16, the efferent endings are greater in number than the afferent, whereas in cells 7, 10, 15 and 99, there are equal numbers of two kinds of the endings. Interestingly enough, the afferents predominate in the remaining cells 9, 115

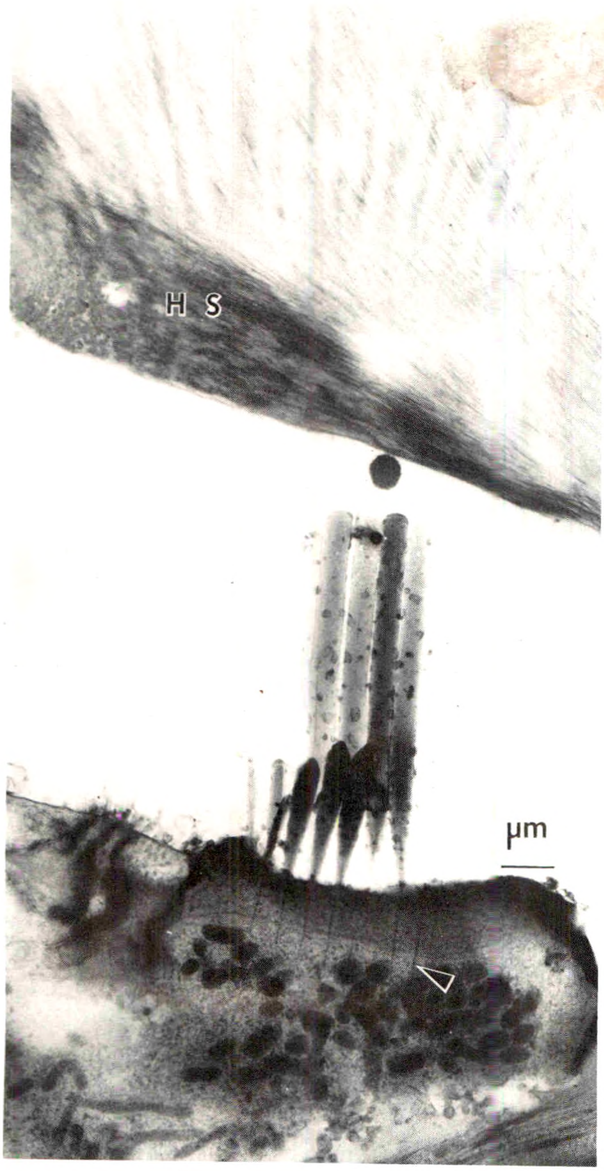


Fig. 4. Entire length of longest stereocilia on inner hair cell clearly seen. Tips of these hairs are not attached to inferior surface of tectorial membrane. Note rootlets (arrow) which completely penetrate cuticular plate and extend into apical cytoplasm. HS - Hensen's stripe.

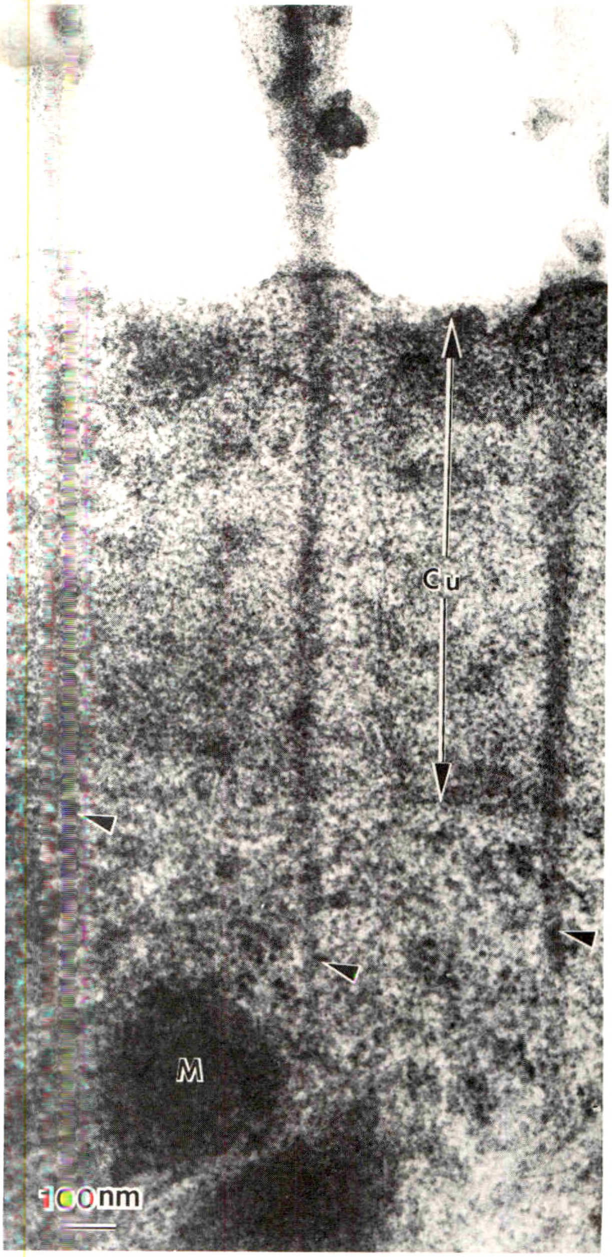


Fig. 5. Higher magnification of rootlets (arrowheads) of IHC. Rootlets penetrate through entire width of cuticular plate (Cu) and extend into apical cytoplasm. Many ribosomes, filaments and mitochondria (M) are present adjacent to rootlets.

and 119. The total number of the efferent endings is 89 and the afferent endings is 87 in these ten cells. Therefore, it seems to indicate that the first row OHC in the third cochlear turn are innervated by nearly equal numbers of efferent and afferent endings, the average number being nine.

DISCUSSION

Application of the HVEM to the study of the guinea pig hearing organ was explored. The main advantage of use of the HVEM is that sharp images of thicker sections can be obtained because of the greater penetrating power of high energy electrons. In the present study, using single or serial thick-sectioning techniques, the fine structure of the tips of the stereocilia and the rootlets as well as the arrangement of efferent and afferent nerve terminals on the bases of the OHC were examined. Through experience, it was determined that the optimum thickness for sections to be studied by HVEM was between 500 and 800 nm. Although it is theoretically possible to observe very thick specimens up to 5 μm in the 1,000 kV HVEM, "it may be reasonable to start by examining relatively thin sections and to increase the thickness only after becoming familiar with the specimens," as suggested by Glauert.[1] We initially examined 200 to 300 nm sections, but found that these often lacked good contrast. Subsequently, thicker sections were examined and the op-

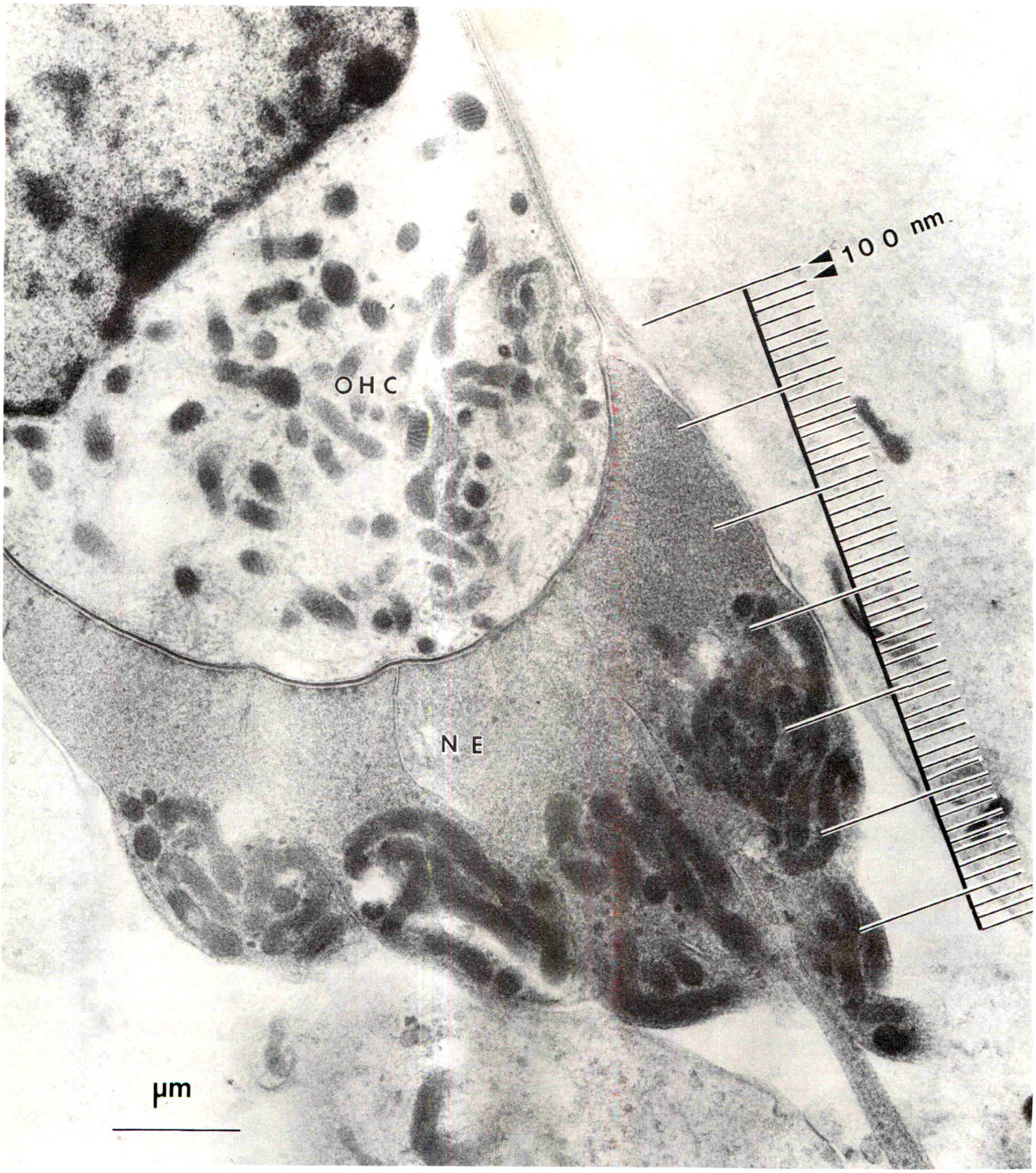


Fig. 6. Electron micrograph of 500-nm thick section showing nerve endings (NE) on OHC. As indicated by scale at right, only six or seven 800-nm thick horizontal sections are needed to cut through entire basal end of cell, whereas more than 50 100-nm sections are needed.

timum range of the thickness was determined. Glauert[1] has noted that "for sections only 500 nm thick, 3-nm resolution is obtained at an accelerating voltage of 500 kV, while for sections 1,000 nm thick it is necessary to raise the voltage to 1,000 kV for the same resolution."

In order to obtain good image contrast, staining techniques for the thick sections must be carefully determined. Sections from specimens which were treated with en bloc staining with 4% aqueous uranyl acetate have better contrast than those from specimens without en bloc staining. The staining time for thicker sections must be increased to allow penetration of the staining solution into the sections.

Using the techniques mentioned above, the present study focused on observations of the ultrastructural features of the sensory hairs and the ar-

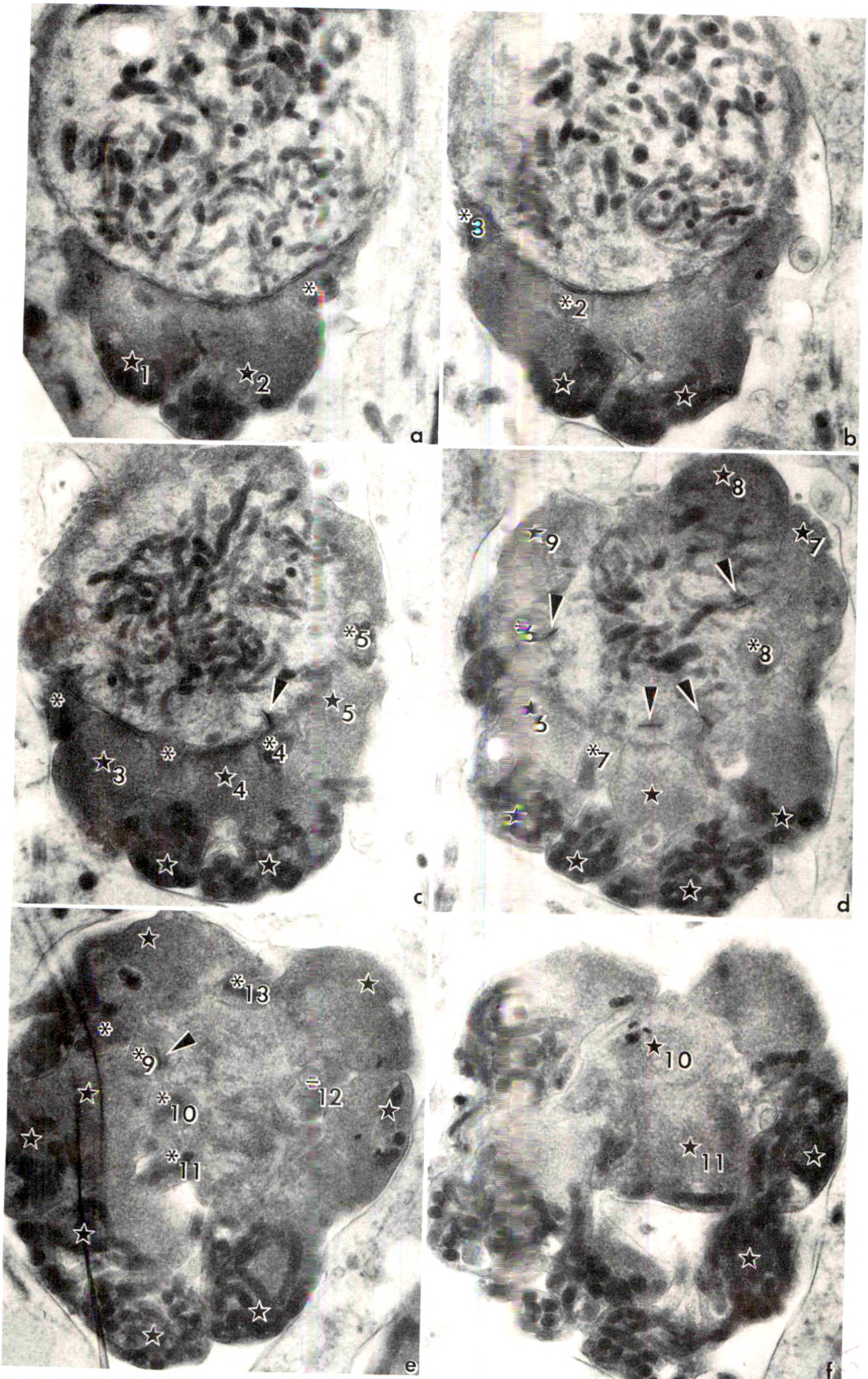


Fig. 7. Serial horizontal sections (800-nm thick) of basal tip of OHC. Stars indicate efferent terminals and asterisks show afferents. a) Two efferents (★1, 2) and single afferent (*1) are seen. b) First afferent (*1) has disappeared and two outer afferents (*2, 3) are visualized. c) Three efferents (★3,4,5) and two afferents (*4, 5) are visible. Synaptic bar (arrow) is present at *4 afferent terminal. d) Hair cell cytoplasm is minimal and four new efferents (★6, 7, 8, 9) and three afferents (*6, 7, 8) are seen. Arrows indicate synaptic bars in cytoplasm. e, f) At these levels, hair cell cytoplasm is no longer visible and central part of region is occupied by five new afferents (*9, 10, 11, 12, 13) and two efferents (★10, 11).

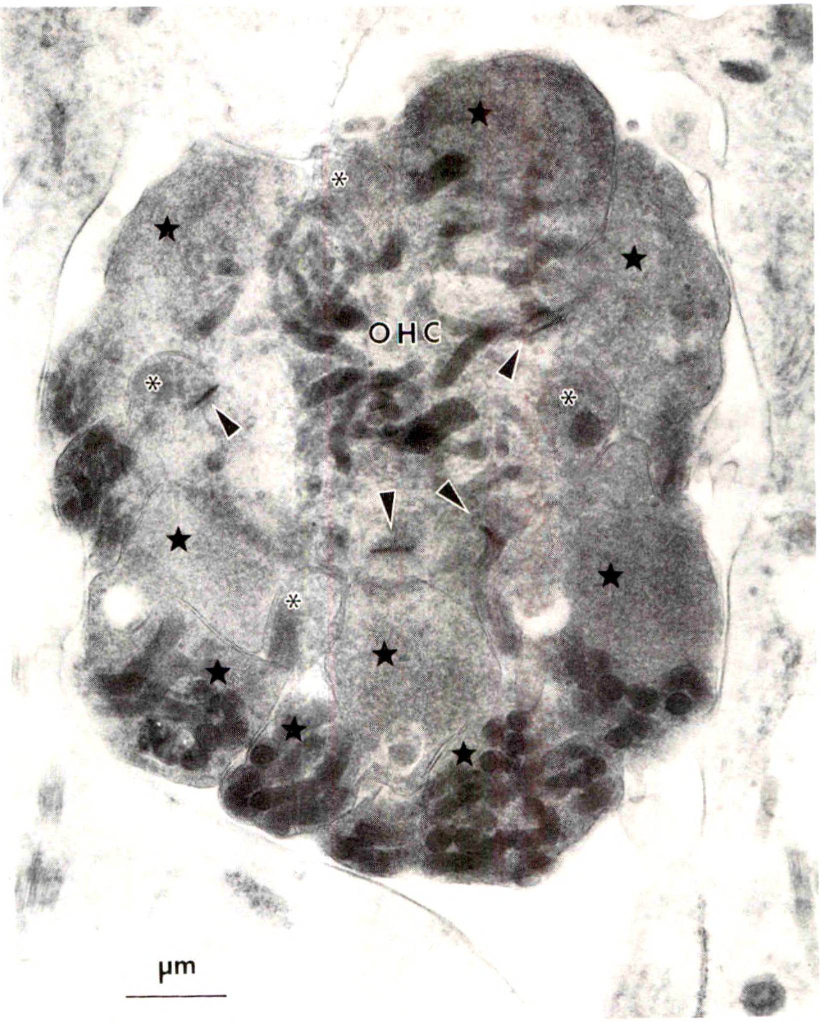


Fig. 8. Higher magnification of Fig. 7d. Efferent (★) and afferent (*) nerve endings are visible around small hair cell cytoplasm (OHC). As this section is very near bottom of hair cell, four synaptic bars (arrowheads) are also present in cytoplasm.

rangement of the efferent and afferent nerve endings on the OHC in the third cochlear turn. The tectorial membrane is quite susceptible to slight changes in osmolarity during preparation for microscopic examination. Thus, the subsequent shrinkage and distortion of the membrane generally results in the separation of the connection between the unit membrane of the hairs and the filaments of the tectorial membrane. Although some scanning electron microscope (SEM) studies[9-15] as well as a few light microscope studies[16,17] have clearly shown the imprints of the hair tips on the undersurface of the tectorial membrane, relatively few TEM studies[18-22] have revealed the distinct attachment of the hairs of the OHC to the tectorial membrane. In the present material, we found that the fixative containing 2% tannic acid produced better results preserving soluble proteins at the contact site between hair tips and tectorial membrane. Kimura[18] has published beautiful electron micrographs of the hair attachment to the tectorial membrane and indicated that there is a narrow light zone immediately outside the unit membrane. In our material such a definite light zone around the tips was not seen. The density of the fine filaments of the tectorial membrane is homogeneous and they are directly attached to the outer leaflet of the unit membrane. It is possible that the differences between our findings and those of Kimura are due to the use of different fixatives; Kimura used 1% buffered osmium tetroxide.

The question of the attachment of the tips of the IHC stereocilia to the tectorial membrane is still unanswered. Although there is little controversy concerning the attachment of the hair tips of the OHC, much disagreement still exists about the stereocilia of the IHC. In the cat's cochlea, Hoshino[10] found some imprints on the undersurface of the tectorial membrane just above the IHC. Tanaka[14] reported a weak adhesion of the hair tips of the IHC to the tectorial membrane using his special "frozen resin cracking method for SEM." Ross[12] also confirmed the direct connection of the hair tips of the

NUMBER OF EFFERENT AND AFFERENT ENDINGS ON THIRD-TURN HAIR CELLS (GUINEA PIG)

Nerve Endings	Cell No.										
	4	5	7	9	10	15	16	99	115	119	Total
Efferent	13	10	7	7	7	6	11	7	10	11	89
Afferent	9	9	7	9	7	6	9	7	11	13	87

IHC of the rat. Recently, using the bulk frozen-hydrated method, Lawrence and Burgio[15] have shown that Hensen's stripe makes contact with the supporting cells around the IHC. They stated that this finding agrees perfectly with Lim's SEM observation.[23] In TEM studies, however, only Iurato[20] demonstrated a definite attachment of the IHC hairs to the filamentous material of the tectorial membrane. In the present study, we were not able to observe any connection between the hair tips and the tectorial membrane at the IHC region, but instead found a narrow fluid space between them.

Using the conventional ultrathin sectioning technique (ie, less than 100 nm), it has been rather difficult to investigate the depth of penetration of the hair rootlets into the cuticular plate. Kimura[18] was first to note that in the squirrel monkey and human, some long rootlets extended into the apical cytoplasm of both IHC and OHC, although the functional significance of these long rootlets was not thoroughly discussed. Engstrom et al[24] have previously stated that "Just how far the rootlets extend cannot be stated with certainty. From our material, it appears that substantial numbers reach as far as the lower surface of the cuticular plate, but whether they continue farther cannot be decided." In our thick specimens, however, more hairs are contained in each section and the basal tip of each rootlet can easily be identified in the cuticular plate. In our material, it was obvious that almost all rootlets of the IHC extended into the apical cytoplasm, whereas the majority of those in the OHC terminated in the midportion of the cuticular plate. As suggested by Flock and Cheung[25] the sensory hairs as well as the rootlets are composed of actin filaments and these filaments are connected to the 30 Å filaments of the cuticular plate. If we assume that these actin filaments provide not only stiffness and elasticity to the hairs, but also the mechanism of mechanical input into the cell, it is conceivable that the two kinds of hair cells may transduce mechanical energy by different means.

It has already been well documented that the sensory hair cells in the cochlea have two types of nerve endings, afferent and efferent. However, very little is known about the ultrastructural details of the terminal arrangements on each OHC in the different rows and cochlear turns, or differences between the IHC and OHC. In 1961, Smith and Sjostrand[26] made the first report by means of a serial thin-sectioning technique and ascertained that there are two types of OHC, A and B. The former cells are innervated by an almost equal number of efferent and afferent nerve endings, whereas the latter possess more afferent endings than efferent. In order to reconfirm this finding, we employed HVEM examination of serial thick sections. Smith and Sjostrand[26] stated that "it was possible to get on each grid good series of 40-50 sections and 12 good series of external hair cells were studied." In our experience, a single ribbon of 12 to 15 sections can be consistently obtained on each single-hole grid. The entire arrangement of nerve endings on a first row OHC is almost completely included within this number of thick sections. In order to determine the utility of the HVEM technique, we initially examined only the first row of OHC in the third cochlear turn. It was concluded that these cells are the type A cells of Smith and Sjostrand.[26] It was confirmed that each cell is innervated by 12 to 24 terminals, the average number being 18, with nine efferent and nine afferent endings. Additional studies should provide further information concerning the pattern of terminals on OHC from different rows and turns as well as those of the IHC.

ACKNOWLEDGMENT — We thank Dr. Barbara A. Bohne for valuable suggestions and Mr. Heishiro Ohta and Eiji Aoyagi for technical assistance.

REFERENCES

1. Glauert AM. The high voltage electron microscope in biology. J Cell Biol 1974; 63:717-48.

2. Takasaka T, Tanaka K, Kawamoto K. Innervation patterns of the cochlear sensory hair cells as studied by serial sections. HVEM Reports of Tohoku Univ. 1978; 1:11-6 (in Japanese).

3. Takasaka T, Sato M, Kaku Y, Tanaka K. An application of high voltage electron microscope in biology. Practica Otologica 1979; 72:679-88 (in Japanese with English abstract).

4. Takasaka T, Kawamoto K. HVEM observations on the sensory hair cells of the inner ear. HVEM Reports of Tohoku Univ. 1980; 2:17-24 (in Japanese).

5. Takasaka T. Inner ear ultrastructure in a high voltage electron microscope. J Otolaryngol Jpn 1980; 83:1391-4 (in Japanese).

6. Takasaka T. Inner ear ultrastructure in a high voltage electron microscope. Shinkei Kenkyu no Shinpo (Advan Neurolog Sci) 1981; 25:777-91 (in Japanese with English abstract).

7. Takasaka T. High voltage electron microscopic study of efferent and afferent nerve endings in the cochlea. Abstr Assoc Res Otolaryngol 1981:80-1.

8. Mizuhira V, Futaesaku Y. On the new approach of tannic acid and digitonine to the biological fixatives. Proc 29th Annu Meet Electron Microsc Soc Am 1971; 494.

9. Kosaka N, Tanaka T, Takiguchi T, Ozeki Y, Takahara S. Observation on the organ of Corti with scanning electron microscope. Acta Otolaryngol (Stockh) 1971; 72:377-84.

10. Hoshino T. Attachment of the inner sensory cell hairs to the tectorial membrane. A scanning electron microscopic study. ORL 1976; 38:11-8.

11. Hoshino T. Contact between the tectorial membrane and the cochlear sensory hairs in the human and the monkey. Arch Otorhinolaryngol 1977; 217:53-60.

12. Ross MD. The tectorial membrane of the rat. Am J Anat 1974; 139:449-82.

13. Lindeman HH, Ades HW, Bredberg G, Engstrom H. The

sensory hairs and the tectorial membrane in the development of the cat's organ of Corti. Acta Otolaryngol (Stockh) 1971; 72:229-42.

14. Tanaka T. Relationship between the organ of Corti and the tectorial membrane. J Clin Electron Microscopy 1973; 6:3-4.

15. Lawrence M, Burgio PA. Attachment of the tectorial membrane revealed by scanning electron microscope. Ann Otol Rhinol Laryngol 1980; 89:325-30.

16. Bredberg G. Cellular pattern and nerve supply of the human organ of Corti. Acta Otolaryngol (Stockh) 1968; Suppl 236.

17. Hawkins JE Jr, Johnsson LG. Light microscopic observations of the inner ear in man and monkey. Ann Otol Rhinol Laryngol 1968; 77:608-28.

18. Kimura RS. Hairs of the cochlear sensory cells and their attachment to the tectorial membrane. Acta Otolaryngol (Stockh) 1966; 61:54-72.

19. Iurato S. Submicroscopic structure of the membranous labyrinth. Z Zellforsch 1961; 53:259-98.

20. Iurato S. Submicroscopic structure of the inner ear. Elmsford, NY: Pergamon Press, 1967.

21. Spoendlin H. Ultrastructure and peripheral innervation pattern in relation to the first coding of the acoustic message. In: DeReuck AVS, Knight J, eds. Hearing mechanisms in vertebrates. CIBA Foundation Symposium. London: Little Brown and Co, 1968:89-125.

22. Ades HW, Engstrom H. Anatomy of the inner ear. In: Keidel WD, Neff WD, eds. Handbook of sensory physiology. Vol 5. Berlin: Springer Verlag, 1974:125-58.

23. Lim DJ. Fine morphology of the tectorial membrane. Arch Otolaryngol 1972; 96:199-215.

24. Engstrom H, Ades HW, Hawkins JE Jr. Structure and functions of the sensory hairs of the inner ear. J Acoust Soc Am 1962; 34:1356-63.

25. Flock A, Cheung HC. Actin filaments in sensory hairs of inner ear receptor cells. J Cell Biol 1977; 75:339-43.

26. Smith CA, Sjostrand FS. Structure of the nerve endings on the external hair cells of the guinea pig cochlea as studied by serial sections. J Ultrastruct Res 1961; 5:523-56.

ANNALS PUBLISHING COMPANY
4507 LACLEDE AVENUE
ST LOUIS, MISSOURI 63108

COPYRIGHT 1983, ANNALS PUBLISHING COMPANY

6.5-8

JOHN RALSTON LINDSAY, MD
1898-1981

EDITORS

ERNEST E. MHOON, JR., MD

ELISABETH F. LANZL, AM

UNIVERSITY OF ... LIBRARY

Supplement 102 — Vol. 92, January-February 1983, No. 1, Part 3

ANNALS OF OTOLOGY, RHINOLOGY & LARYNGOLOGY
ANNALS OF HEAD & NECK MEDICINE & SURGERY

CONTRIBUTORS

Robert A. Butler, PhD
Professor
Departments of Surgery (Otolaryngology) and
Behavioral Sciences
University of Chicago

César Fernández, MD
Professor Emeritus
Department of Surgery (Otolaryngology)
University of Chicago

John Fredrickson, MD
Chairman
Department of Otolaryngology
Washington University School of Medicine
St. Louis

Robert I. Kohut, MD
Director
Division of Otolaryngology
Bowman-Gray School of Medicine
Winston-Salem, North Carolina

Elisabeth F. Lanzl, AM
Editor
Franklin McLean Memorial Research Institute
University of Chicago Hospitals

Mitchell Marion, MD
Resident, Otolaryngology
University of Indiana
Indianapolis

Gregory J. Matz, MD
Professor of Surgery
Chairman, Section of Otolaryngology
University of Chicago

Ernest E. Mhoon, Jr, MD
Assistant Professor of Surgery (Otolaryngology)
Assistant Dean of Students, Division of the
Biological Sciences
University of Chicago

Ralph F. Naunton, MD
Director
Communicative Disorders Program, NINCDS-NIH
Bethesda, Maryland

Harold F. Schuknecht, MD
Chief of Otolaryngology
Massachusetts Eye and Ear Infirmary
Boston

JOHN RALSTON LINDSAY, MD

1898-1981

EDITORS

ERNEST E. MHOON, JR., MD
ELISABETH F. LANZL, AM

From the Department of Surgery, Section of Otolaryngology, The University of Chicago.

ACKNOWLEDGMENTS

This supplement was prepared with the advice and encouragement of the late Dr. Ben Senturia. We are grateful to the speakers at the First Annual John R. Lindsay Scientific Lectures for their participation. We are also grateful to Dr. Paul H. Ward for his generous support of the lectures. Mrs. Lindsay allowed us access to her husband's papers and to his library. Her encouragement of this project was invaluable.

We are indebted to Dr. Raul Hinojosa, who meticulously undertook the task of checking the long list of Dr. Lindsay's publications. Dr. Hinojosa provided most of the illustrations which appear in this supplement; Dr. César Fernández and Dr. Henry Perlman also kindly contributed figures. Dr. Fernández, Dr. Hinojosa, and Dr. Robert Butler gave valuable advice on various aspects of the preparation of the text. The preparation of the text for publication would not have been possible without the help of Mrs. Eleanor Smith and Mrs. Shirley Belanger. The manuscripts were typed in their final form by Mrs. Donna Freeman.

We appreciate the support of Dr. Gregory J. Matz, Professor of Surgery and Chairman of the Section of Otolaryngology, University of Chicago.

CONTENTS

Introduction 5
Obituary 7
Interviews with John Lindsay 8
John R. Lindsay: Clinician, Teacher, Otopathologist. H. F. Schuknecht, MD 12
Otoneurology. J. M. Fredrickson, MD 17
The Clinical Research of John Lindsay. R. I. Kohut, MD 20
Pioneers in Research in Otolaryngology at the University of Chicago. C. Fernández, MD 23
Basic Science Researchers in Otolaryngology at the University of Chicago. R. A. Butler, PhD 27
Clinical Research in Otolaryngology at the University of Chicago. R. F. Naunton, MD 30

Appendix: Publications by John R. Lindsay

  Journal Articles 33
  Books and Book Chapters 36

INTRODUCTION

John Ralston Lindsay, distinguished otolaryngologist, teacher, researcher, leader, and former Chief of Otolaryngology at the University of Chicago, died on December 21, 1981, following a chronic illness. He dedicated his life to the advancement of knowledge and education in otolaryngology and did so with a rare combination of warmth, caring, generosity, guidance, leadership, and strength. A poignant example of his concern for others was his request that his memorial service be postponed until the spring, when travel conditions in the Chicago area would be more favorable for those wishing to attend. His request was honored on April 30, 1982, when a memorial service was held at Rockefeller Chapel on the campus of the University of Chicago. As a tribute to his outstanding contributions to teaching and research in otolaryngology, the first annual John Ralston Lindsay Scientific Lectures were held in the Billings Hospital auditorium just preceding the memorial service. Six distinguished otolaryngologists and researchers whose successful careers were directly influenced by the leadership and guidance of Dr. Lindsay presented papers on specific aspects of Dr. Lindsay's contributions.

Dr. Ernest Mhoon, Assistant Professor in the Section of Otolaryngology and Assistant Dean of Students in the Medical School of the University of Chicago, served as chairman and moderator for the session, which was opened by Dr. Harold F. Schuknecht, Professor and Chairman of Otolaryngology at the Massachusetts Eye and Ear Infirmary. Dr. Schuknecht was a Lindsay resident from January 1946 to January 1949, and he served on the Otolaryngology faculty at the University of Chicago from 1949 to 1953. The second speaker was Dr. John Fredrickson, until recently Professor of Otolaryngology at the University of Toronto, and a Lindsay resident from July 1960 to December 1963. He was a member of the Otolaryngology Faculty at the University of Chicago from January 1964 to September 1965, and is now Professor and Chairman of Otolaryngology at Washington University in St. Louis. Dr. Fredrickson was followed by Dr. Robert Kohut, Professor and Chairman of Otolaryngology at the Bowman-Gray School of Medicine, who was a Lindsay resident from 1961 to 1964 and an Otolaryngology faculty member during the following year.

Two of the remaining speakers are still at the University of Chicago. Dr. César Fernández, Professor Emeritus in the Section of Otolaryngology, joined the faculty at the University of Chicago on March 1, 1954, and continues to be active in teaching and research. Dr. Robert A. Butler, Professor of Behavioral Sciences and in the Section of Otolaryngology, became a member of the Otolaryngology faculty on May 1, 1957.

The final paper was delivered by Dr. Ralph F. Naunton, Director of the Communicative Disorders Program at the National Institute of Neurological and Communicative Disorders and Stroke. Dr. Naunton served on the Otolaryngology faculty at the University of Chicago from August 1954 to June 1980. He succeeded Dr. Lindsay as Chairman of Otolaryngology in 1964 and served in that capacity until 1979. Shortly thereafter, he assumed his present position.

The six papers presented in these first John Ralston Lindsay Scientific Lectures describe specific aspects of Dr. Lindsay's long and productive career in otolaryngology. Among the topics discussed are his many contributions to patient care, teaching, and research. No better presentation of these accomplishments could have been made by anyone other than those who were direct recipients of his genius.

B 24815

JOHN R. LINDSAY, 1898-1981

In the fall of 1928, Dr. John R. Lindsay arrived at the University of Chicago, where he was to become one of the foremost otolaryngologists of his time. He would devote his life to understanding the diseases of the human ear, in the hope of breaking down the barrier of silence of the deaf, whom he described as living in "an awful world of separateness where life chaotically moves before them." Dr. Lindsay came to the University of Chicago after completing his otolaryngology residency at McGill University, Montreal, Canada.

Otolaryngology at the University of Chicago was then just beginning, and after only a few years, Dr. Lindsay was made head of this section. He distinguished himself as a highly respected chairman, a clinician with superb diagnostic and surgical skills, and, above all, a devoted teacher. Over the next 35 years, he became an internationally recognized otopathologist. He made a number of important contributions, including his studies on the pathology of Menière's disease, suppuration of the petrous apex, the pathology of cholesteatoma, and the preoperative and postoperative pathology of otosclerosis. He will also be remembered for his studies on ossicular chain and vestibular physiology, positional nystagmus, and profound sensorineural deafness. This work is described in more than 180 publications, which directly influenced the rules that govern the present-day practice of clinical otology.

At the University of Chicago, Dr. Lindsay organized a residency program which was among the best in the United States. He trained many outstanding physicians, twelve of whom became directors of otolaryngology programs at various universities.

Dr. Lindsay was a member of the Chicago and the American Medical Associations; the American Otological Society, Inc.; the Institute of Medicine of Chicago; the American Broncho-Esophagological Association; the American Laryngological Association; the Collegium Oto-Rhino-Laryngologicum Amicitiae Sacrum; and the American College of Surgeons.

His services to medicine beyond the boundaries of the University of Chicago were considerable. He participated in organizing the National Temporal Bone Bank under the auspices of the Deafness Research Foundation. He was president of both the American and the Chicago Laryngological and Otological Societies (1947), chairman of the Otolaryngological Section of the American Medical Association (1955-56), president of the American Laryngological, Rhinological and Otological Society (1961-62), and president of the American Academy of Ophthalmology and Otolaryngology (1964). Dr. Lindsay also was chairman of the Otolaryngology Training Grant Committee (1959-63) and served as a member of the Council, National Institute of Neurological Diseases and Blindness (1965-68), both under the United States Public Health Service. He was editor of the *Year Book of Ear, Nose and Throat;* a director of the American Board of Otolaryngology; a trustee of both the Beltone Institute for Hearing Research and the Central Bureau of Research of the American Otological Society, Inc.; as well as an advisor for the Deafness Research Foundation.

Dr. Lindsay's achievements brought him many honors, including the gold key for special services, awarded by the American Academy of Ophthalmology and Otolaryngology; the George E. Shambaugh prize in otology, given by the Collegium Oto-Rhino-Laryngologicum Amicitiae Sacrum; the Award of Merit of the American Otological Society, Inc.; and an honorary Doctor of Medicine degree from the University of Uppsala, Sweden. In 1964, the University of Chicago honored him by appointing him the Thomas D. Jones Professor of Surgery.

Dr. Lindsay was Chairman of the Section of Otolaryngology, Department of Surgery, at the University of Chicago from 1930 through 1965. He remained on the staff of the Otolaryngology Section after he retired as chairman and was active in the department up to the time of his death.

ERNEST E. MHOON, JR, MD
MITCHELL MARION, MD
GREGORY J. MATZ, MD

INTERVIEWS WITH JOHN LINDSAY

In the last months preceding his death, Dr. Lindsay allowed me to meet with him for a series of interviews. Our objective was to gain an appreciation of the process by which the field of otolaryngology had emerged and, at the same time, to catch a glimpse of the wisdom and insight of Dr. Lindsay.

These interviews, a shortened version of which is presented here, took place in Dr. Lindsay's office at the University of Chicago during November and early December 1981. The weekly sessions generated a total of six hours of recordings on tape. I am indebted to Eleanor Smith who patiently transcribed the tapes and typed the drafts and final version, and to Elisabeth Lanzl for her gifted skills in helping to organize and edit the text.

It is a delight and honor for me to have been able to meet such a prominent leader in our field.

Mitchell Marion, MD

P23797

Q Tell me something about your early life. Where were you born?

A I guess Canada is good enough; Renfrew, Ontario, Canada. That's a place of about 10,000 people, near the Ottawa River. My mother died when my sister was born. I was only four years old and just barely remember her. After that, I lived with my grandparents, my father's parents, for many years.

I went through high school at a very young age — too young. As a matter of fact, I finished high school the year the First World War started. My older brother and I both had eye injuries and had to stay home during the war. My left eye was shot with a wooden arrow. Therefore, I've been dependent on my right eye for vision since I was nine years old. So, from 1914 through the war to 1919, the two of us were working my father's land. At the end of the war I went into medical school, and I got out in 1925.

Q How did you decide to become a doctor?

A A friend of the family got to talking to my father, saying that my brother and I should be doctors. My father encouraged us without our knowing it. He encouraged me to go to McGill, and I went through the six-year medical program there. My brother had to stay at home to help my father, who was then in his 60s and couldn't look after all of his land by himself.

Q How did you become interested in otolaryngology?

A I felt I didn't know much, putting it practically. I had taken my internship at Ottawa Civic Hospital. The following June, I went to work with a country doctor who was in general practice and did a lot of surgery. He was active in politics and was away a great deal, and I was left high and dry a lot of the time except when he would come home on weekends. This made me realize that I didn't know much about cases that had to be handled day by day. From what I saw, I thought I had better stick to a specialty because there was so much to learn in medicine. I decided to get out of the country town and accepted a residency in otolaryngology at the Hospital for Sick Children in Toronto, a well-known hospital. During that year in Toronto I did general ear, nose, and throat work. Every Tuesday and Thursday afternoon I would have 12 tonsillectomies booked. These were all children. You can imagine how many I did; that was one of the main occupations of otolaryngologists in those days. After one year, I went back to McGill to complete my otolaryngology residency.

Q How did the Section of Otolaryngology at the University of Chicago get started?

A After my residency, Dr. Dallas Phemister, who was Chief of Surgery at the University of Chicago, offered me a position in otolaryngology. The University Medical Center had just opened in late 1927, and I came to the University as an Assistant Professor in the new Section of Otolaryngology in 1928. In 1929, I brought Dr. Gordon H. Scott to the University as a staff member in ENT; and when I left for Europe in 1931 to study, he became the Acting Chairman until I returned. Dr. Theo Walsh was also one of the original members of our staff, along with Dr. Henry Perlman. Dr. M. M. Hipskind was the first resident to be graduated from the otolaryngology residency program, which started in 1933.

Q How did you become interested in academic medicine?

A That came by degrees; it didn't come quickly. I knew that Dr. Phemister was anxious to get research going. He knew that there were defects, a lot of defects, in the practice of surgery, and he knew there must be defects in ear surgery. He encouraged me to learn more about the ear and offered me a year in Europe on salary. I went to Europe in 1931.

I spent most of that time in Zurich, Switzerland, with Dr. F. R. Nager, who was a very well-known otolaryngologist. He had his practice in a separate house just down the hill from the university buildings. In that house he also had his office as the chief of ear, nose, and throat at the university, and that is where I worked. Every time he had something worthwhile, he would call me in to show it to me. I would be in the next room, in his temporal bone laboratory, and he would go over cases with me. This is where I really got started in pathology and where I became interested in temporal bone research. He had a big collection of temporal bones, and this man had learned the art of processing them. As far as I know, he was the first to develop a temporal bone library.

Q Did Dr. Nager show you how to cut a temporal bone and remove it?

A No, but I would watch his technician do this in the room where I was working. She cut the bones, and then Dr. Nager would look at them; that was the routine. He had hundreds of slides. I would go over them and I would bring things to him that I couldn't understand.

Q Have you ever thought that if you had not gone to Europe you wouldn't have gotten started in otopathology?

A Yes. I don't think Dr. Phemister was quite sure what he was sending me to Zurich for. He just wanted me to go and work under Nager. Nager's main contribution was the laboratory full of prepared temporal bone sections.

Q When you returned to the University of Chicago, you began to establish a temporal bone research program. Your early investigations were on the pneumatization of the temporal bone and otitic meningitis?

A Oh yes, that was very important. When I got back from Europe, I started to save, from the morgue, every ear I could get my hands on — or anybody else could get their hands on. The processing took about a year after you got the ears; then you could study what was going on.

We didn't have antibiotics in those days. Many children died from the meningitis that resulted from otitis media. In fact, my father died in 1930 of meningitis that followed acute suppurative otitis media. If I had known in 1930 what I knew later on about pneumatization, I could have saved him. Patients died because nobody knew how to diagnose the cases clearly. I used to get such cases, and you couldn't cure them by doing a mastoidectomy — they would die. I wanted to find out why they died, and I spent about a quarter of a lifetime studying this problem. From temporal bone sections, we were able to trace pneumatized pathways going right into the apex past the inner ear, and it was a question of mapping these pathways so that the course of the infection could be followed. All of this was just beginning to be developed in the 1930s.

The majority of patients with middle ear infections would get well after the middle ear was drained adequately. The first thing you would see was whether the eardrum was bulging. You could tell by looking whether there was fluid or pus; then you would let it drain, and the infection would take around two weeks to run its course. But you would follow it day by day, and if it was obviously getting worse, you would need to clean out the mastoid and apex cells, to an extent that varied from case to case. We didn't use a microscope for mastoidectomies; we didn't have one. If you had a good pair of eyes, the cells were easily visualized.

Some of the patients had meningitis by the time we saw them. Meningeal breakthrough was very dangerous — you would have to watch for signs and learn how to take x-rays. If the x-rays showed that the air cells extended around the inner ear to the apex of the petrous bone, the apex was pneumatized, and if pneumatized, it was likely to become filled with pus. These were the cases you worried about.

Often, when you followed a patient with otitis media, there came a time when you were on pins and needles as to whether you were going to have to operate. I always admired George Shambaugh's father, who was the top ear man in Chicago. His advice was, "Wait a while and see what happens," and many times the patient would get well.

Q Tell me about the origin of stapes surgery.

A During World War II, I saw a patient who had cracked the rim of the stapes, and the question was whether the patient would get worse or better. In fact, the patient's hearing did not suffer. At that time, people couldn't imagine doing anything to the stapes without killing the ear.

We were dissecting temporal bones in the laboratory at that time. You know, I began to see that you could do more than you realized before, without damaging the ear; and I became convinced of the possibility of doing stapes surgery. At an otosclerosis symposium in 1956, someone mentioned that he had done a stapedectomy, and that the patient's hearing had improved. That was Dr. John Shea, who became very prominent doing stapedectomies.

Q Who taught you to do stapedectomies?

A I practiced on temporal bones for many years; that is the way you learn.

Q Besides doing ear surgery, did you do much head and neck surgery?

A I never did very much; it wasn't there to do. We saw very little head and neck cancer; that was a small problem compared to the complications of middle ear suppuration. We were spending most of our time on children with middle ear infections who didn't get well.

Q What do you consider your most important publication?

A Oh, heavens, I never felt that any one paper was very important. You finally got something that you decided was worth putting on paper, and then you'd be conscious of other things that had not been explained. This bothered me. I remember that, even when I was taking a long vacation, we would be out at the lake, and I would decide that I had to leave to go to the library. There is always something that still has to be worked on.

Q That is true. However, you contributed more than 200 major publications to our specialty; surely you must be proud of this accomplishment.

A It never occurred to me to be proud of a paper. I was lucky if a paper was accepted on the first try. I wasn't a good writer, and I didn't pay any attention to the rules of grammar. You learn to write in a way that can't be misunderstood; at least, you hope to be understood. And when you write something, you want it to be correct.

Q Finally, Dr. Lindsay, can you comment on the significance of research and its role in our specialty?

A There is a tendency to become stagnant unless you keep up with research that has an influence on your specialty. That is the same with any specialty in medicine. At the University of Chicago, research has always been emphasized. Residents develop an interest in research because they can see it going on right around them, and they have a chance to learn what research is. In this way, they receive a fuller education.

Some people are naturally interested in doing high-quality research, making a reputation through what they do, what they produce. Then there are others who get their satisfaction out of making big money. There seem to be two sets of ideals, one set being for those who make the big money and just can't resist it. Money is useful, of course, but it is much more satisfying to go after knowledge.

JOHN R. LINDSAY: CLINICIAN, TEACHER, OTOPATHOLOGIST

Harold F. Schuknecht, MD

John Ralston Lindsay, a Canadian by birth, graduated from McGill University School of Medicine in 1925, at the age of 26 years. After three years of postgraduate training in Ottawa, Toronto, and Montreal, he was appointed assistant professor in otolaryngology on the full-time faculty of the newly established School of Medicine at the University of Chicago. Here he came under the influence of Dallas Phemister in surgery, Paul Cannon in pathology, George Dick in medicine, and many other members of a very distinguished faculty.

The scholarly attitude toward medicine that was an inherent part of John Lindsay's character was strengthened by the close working relationships he established with his peers, including Walter Palmer, Henry Ricketts, Lowell Coggeshall, Edward Compere, Howard Hatcher, Huberta Livingstone, William Adams, Lester Dragstedt, Alexander Brunschwig, and Eleanor Humphreys, to mention a few. All became leaders in their respective fields. These exceptionally dedicated and talented faculty members were of a common mind in believing that physicians have an important role to play in biomedical research. Their philosophy dictated that physicians who know the clinical expressions of disease are best able to establish and maintain a relationship between clinical medicine and research.

Two years after arriving at the University of Chicago, John embarked upon a nine-month study tour of Europe that included six months under the tutelage of Prof. F. R. Nager at the University of Zurich, followed by three months in Vienna. One of his objectives in the Zurich visit was to study Nager's temporal bone collection.

When he returned to his work at the University of Chicago, John Lindsay was acutely aware of the deficiencies in current knowledge of otology. He was convinced that a knowledge of pathology is basic to an understanding of disease processes and to their intelligent treatment. The University of Chicago seemed to him to be the ideal place to develop a temporal bone laboratory. The environment for scientific endeavor that was so carefully developed and nurtured there provided the perfect environment for his studies on ear pathology. The temporal bone laboratory which he developed was only the second in the United States. The first, located at Johns Hopkins University, was under the direction of Stacy Guild, who was succeeded by George Nager, son of John's mentor in Zurich. Although a primary function of the laboratory was to elucidate the pathological basis of human otologic disease, it also provided essential support for animal experiments.

One of the most serious problems confronting otologists at that time was suppuration in the petrous pyramid. The numerous deaths from this disease provided a ready source of temporal bones. John Lindsay's work on the pathology of progressive bacterial invasion of the petrous bone remains the single classic study of the pathology of this disease. In 1938, he first reported on his surgical experience with such cases,[1] and he supported his concepts regarding surgical approaches with his studies of human temporal bones. The principal cause of death was abscess formation in the petrous apex; the surgical problem was how best to drain the abscess.

Paralleling these investigations, he began detailed work on pneumatization of the temporal bone. John defined the apical area as "that part of the pyramid lying anterior to the cochlear capsule and internal auditory meatus but medial to the carotid canal. The term 'peritubal' is reserved for the cells surrounding the eustachian tube and lying lateral to the carotid canal."[2] He showed that the petrous apex is pneumatized in 21% of temporal bones; in 7% there is superior apical pneumatization from the mastoid, and in 14% a more inferior pneumatization from the middle ear (Fig. 1). A very important clinical application resulted from studies with the radiologist Paul C. Hodges, who had a special interest in radiography of the skull.[3] They combined these investigations on pneumatization, as well as the postmortem temporal bone studies on petrous suppuration (Fig. 2), with radiological observations to create an award-winning exhibit in 1939 for the annual sessions of the American Medical Association and the American Academy of Ophthalmology and Otolaryngology.

John taught that an abscess of the apex of the petrous bone is usually not accessible from the mastoid, and that it is most often a closed-space abscess. He developed a surgical approach to the apex which was a combination of techniques recommended by Eagleton,[4] Ramadier,[5] and Kopetzky and Almour.[6] He taught that a tract from the mastoid to the apex should first be sought, and that, if this failed, an approach from the middle ear is indicated. This ap-

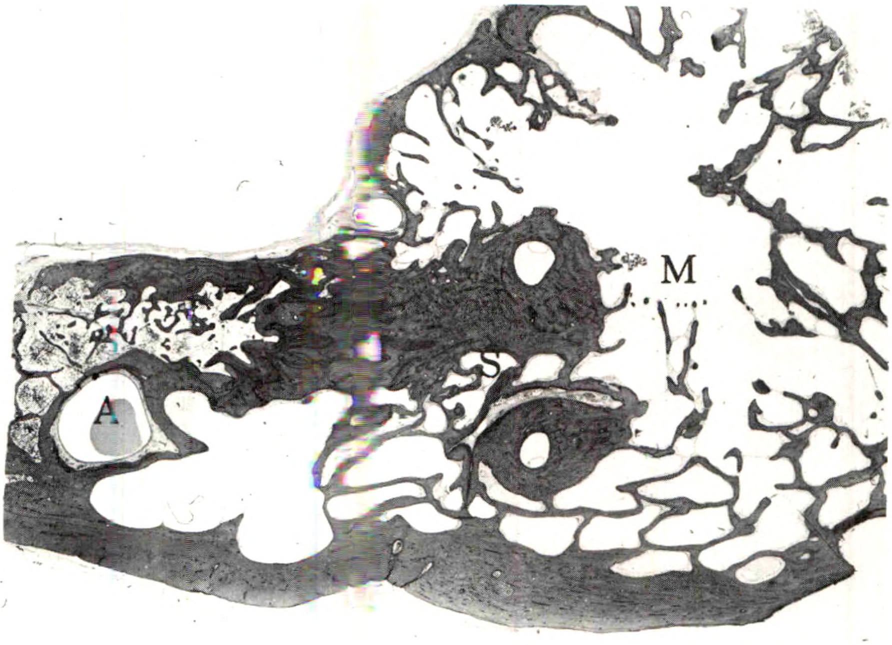


Fig. 1. Horizontal section showing pneumatization from superior aspect of temporal bone. Air cells extend into superior portion of petrous apex. M - Mastoid; S - Subarcuate fossa; A - Petrous apex.

proach is anterior to the cochlea and includes removal of the epitympanic process, part of the zygomatic root, the anterior wall of the external auditory canal, and the tensor tympani muscle.

I was to see my one and only case of abscess of the petrous apex when I was a resident, in 1949. I assisted Dr. Lindsay in the surgery, and I well remember that the abscess in this case was drained from the mastoid via the subarcuate tract. Fortunately, this grim disease that had plagued physicians for centuries was soon to be controlled with the advent of chemotherapy and, later, antibiotics. Nonetheless, surgical drainage is still necessary for some patients, particularly in the less-developed countries.

In 1942, John reported on his first case of idiopathic endolymphatic hydrops under the title "Labyrinthine Dropsy and Ménière's Disease."[7] This paper appeared barely four years after the first description of the pathology of this disease, in 1938, by Hallpike and Cairns[8] in England and by Yamakawa[9] in Japan. During the ensuing three decades, John published many papers on the pathology, diagnosis, and treatment of Menière's disease. The excellent histologic studies of human temporal bones in his laboratory provided the otologic world with graphic documentation of the dilatations, distortions, ruptures, and degenerative changes occurring in the membranous labyrinth in this disease (Fig. 3). John reasoned that the over-accumulation of en-

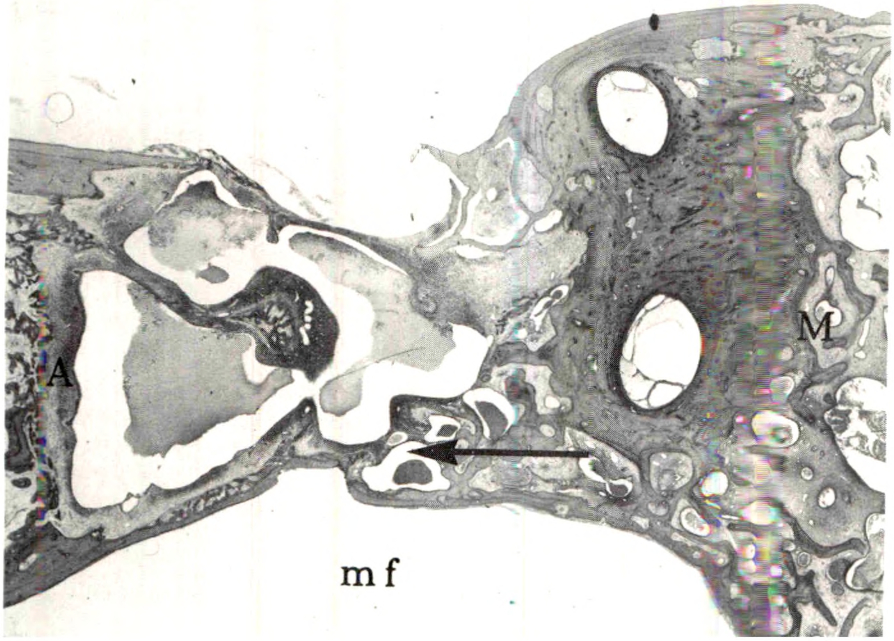


Fig. 2. Photomicrograph showing inflammatory process extending into petrous apex. A tract of pneumatic cells (arrow) filled with exudate extends from mastoid (M) to petrous apex (A) medial to arcuate eminence. mf - Middle cranial fossa.

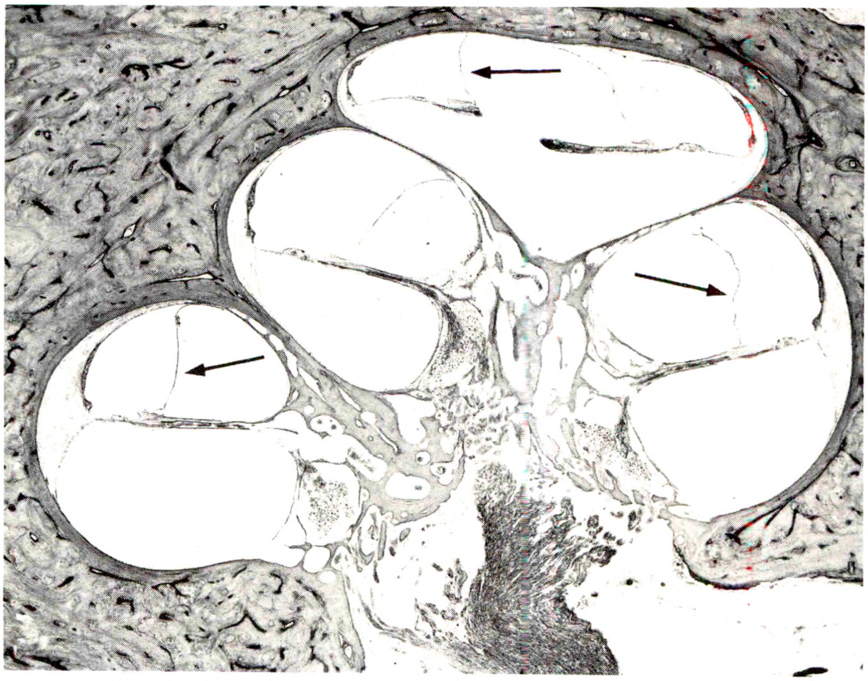


Fig. 3. Section of cochlea at midmodiolar level showing dilatation of cochlear duct in all turns (arrows). There is no apparent degeneration of cochlear ganglion cells or of cochlear nerve fibers.

dolymph might be caused by a failure of resorption, a function then generally ascribed to the endolymphatic sac. In 1947, in an attempt to produce endolymphatic hydrops, he surgically obliterated the endolymphatic sacs and ducts of monkeys, but found no hydrops by 3½ months after surgery.[10] A similar experiment on cats was reported by Lindsay, Neff, Perlman, Kimura, and myself in 1952[11] and 1953.[12] John was on the right track, but we now know that we underestimated the postoperative survival time required for the development of endolymphatic hydrops in these animals.

During these early years, John enjoyed the professional camaraderie of an exceptionally competent staff which included Henry Perlman, Heinz Kobrak, Gordon Scott, and many outstanding residents, among them Myron Hipskind, Meyer Fox, and Bruce Proctor. All later became distinguished otolaryngologists.

Although John's emphasis was on temporal bone pathology, he had many other medical interests, including sinus disease[13] as well as diseases of the esophagus[14] and of the upper airway.[15] He also had an intense interest in otosclerosis. The pathology of otosclerosis had been well known for over 30 years, but the disease generated renewed interest with the development of the fenestration operation by Sourdille in 1937[16] and Lempert in 1938.[17] Julius Lempert was a superb surgeon and entrepreneur, but he leaned heavily on John for help in understanding the surgical pathology of otosclerosis. Julius and John established a close personal and professional relationship which continued until Julius's unfortunate death from Alzheimer's disease in 1967.

One of the problems in the early years of fenestration surgery was bony closure of the fenestra nova ovalis (Fig. 4). In 1946, John described the histopathologic findings after fenestrations were performed in monkeys.[18] He showed that the "fistula remains open only by virtue of the union which occurs between the membranous labyrinth and the covering flap to the exclusion of osteogenic tissue." I remember John telling me, with a chuckle, that the monkeys would remove their own ear dressings at exactly the appropriate postoperative time. These experiments provided the basis for the development of a more successful fenestration procedure. The drilling was done so as to place the fenestra on a dome of the lateral canal; thus, the membranous canal came into contact with the tympanomeatal flap.

John had excellent results with fenestration surgery. In those days, the operation was performed with the aid of a six-power loupe, the surgeon standing with head bent over the operative field. An assistant was needed for irrigation and aspiration, and it was my pleasure to perform this function for John for a full year. Even though the task was sometimes arduous, the opportunity to work with him was a privilege, and I learned much about anatomy, surgical technique, and discipline that was to serve me well in my own career.

John was interested in the broad field of vertigo,[19] particularly in positional vertigo.[20] He was fascinated with the clinical manifestations of paroxysmal positional vertigo, but was distressed that his temporal bone studies did not reveal a logical pathologic correlate. He exhibited real skepticism when I put forth the concept of cupulolithiasis, and I think he never fully accepted the idea.

Throughout his career, John presented numerous

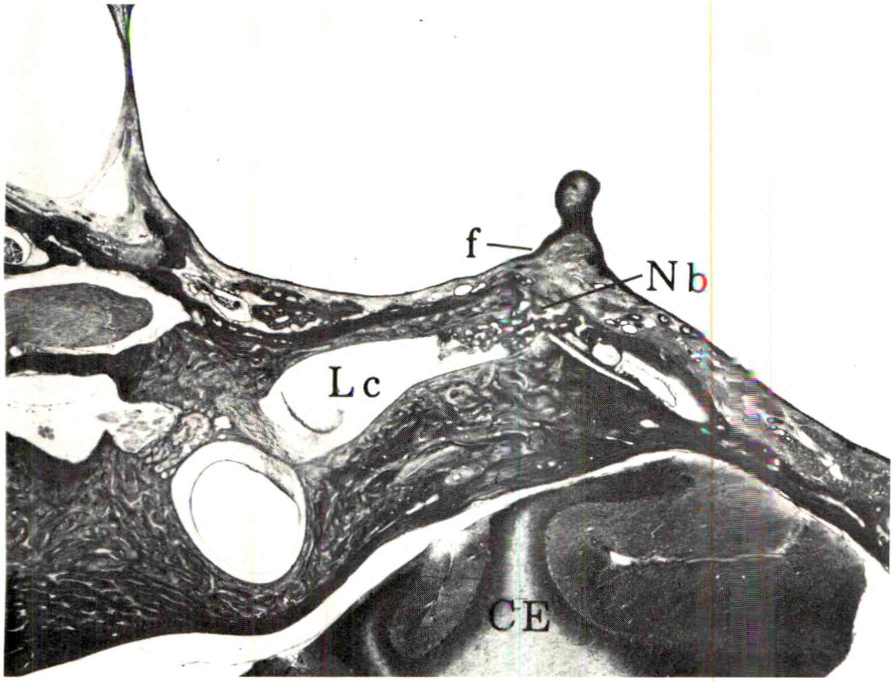


Fig. 4. Fistula in left ear of monkey number 11.[18] Callus (Nb) developed from both periosteal and endosteal surfaces, closing fistula. Cutaneous flap (f) from the posterior wall of external auditory meatus failed to prevent regeneration of periosteal bone. Lc - Lateral semicircular canal; CE - Cerebellum.

descriptive reports on the pathology of otologic diseases, often in coauthorship with his residents or research fellows. It was his way of indoctrinating young men and women into the scientific method, with the expectation that some of them would go into academic otolaryngology.

Let me list for you some of the other otologic disorders to which he added new knowledge through clinical experience, laboratory research, and temporal bone studies. I will also mention some of his collaborators, a list of whom reads like a Who's Who in academic otology.

From 1935 to 1941, John published a series of papers with Henry Perlman and Heinz Kobrak on subjects such as middle ear muscle reflexes, the utriculolymphatic valve, Paget's disease, the relation of the inner ear spaces to the subarachnoid space, and auditory fatigue. Shortly thereafter, he produced two excellent articles with Bruce Proctor, one on tuberculosis of the ear[21] and another on sequestration of the osseous labyrinth.[22]

There were papers on the pathology of rubella deafness[23] with Spencer Harrison; positional vertigo[24] with Garth Hemenway; labyrinthine hydrops[25] with Gustav von Schulthess; mumps,[26] multiple sclerosis,[27] and cytomegalic inclusion disease[28] with Paul Ward; neomycin deafness[29] with Leonard Proctor; fracture of the temporal bone[30] with John Fredrickson; sensorineural hearing loss in otosclerosis,[31] radiation-induced carcinoma,[32] and congenital deafness[33] with D. D. Beal; Menière's disease[34] with Robert Kohut; Paget's disease[35] with R. H. Lehman; inner ear anomalies[36] with Ralph Naunton and Galdino Valvassori; histiocytosis *X*[37] with Arnold Cohn; inner ear concussion[38] with Joan Zajtchuk; herpes zoster oticus[39] with Joan Zajtchuk and Gregory Matz; Apert's syndrome[40] with Owen Black; presbycusis[41] and acoustic neurinoma[42] with Fumio Suga; and Reye's syndrome,[43] profound deafness,[44] and deafness in renal dysplasia[45] with Raul Hinojosa. In 1976, he coauthored an important contribution to the understanding of recurrent meningitis and labyrinthine gusher with Hipskind and Valvassori.[46] In the late 1940s and early 1950s, I was a coauthor of a paper with John on intracranial complications of ear disease,[47] another on benign cysts of the paranasal sinuses,[48] and two papers on experimental blockage of the endolymphatic duct.[11,12]

There are others who have worked with John Lindsay, some in the laboratory, some in clinical endeavors. Among them are César Fernández, Robert Kimura, Joseph Hind, George Allen, J. S. Riesco-McClure, George Connor, René Alzate, Robert Butler, and William Ironside. It would be impossible to mention all those who have benefited from an association with John Lindsay.

When discussing a colleague's presentation, John was always careful not to challenge or offend, and his comments had a constructive rather than a critical tone. In the presence of controversy, he was always a calming force. In the eight years that I was closely associated with him, three years as resident and five years on the faculty of the University of Chicago, as well as during the subsequent 30 years that we were fellow academicians, I never heard him use profanity, deride his colleagues, criticize unfairly, or make a derogatory remark. He was the most universally respected and loved man in otolaryngology. He was a scholar and a perfectionist, but he knew better than to expect this of us. He gave much to his fellow men, but expected little in return.

REFERENCES

1. Lindsay JR. Suppuration in the petrous pyramid. Ann Otol Rhinol Laryngol 1938; 47:3-36.

2. Lindsay JR. Petrous pyramid of temporal bone. Pneumatization and roentgenologic appearance. Arch Otolaryngol 1940; 31:231-55.

3. Hodges PC. An apparatus for stereoscopic roentgenography of the skull. A J R 1939; 42:921.

4. Eagleton WP. Unlocking of the petrous pyramid for localized bulbar (pontile) meningitis secondary to suppuration of the petrous apex. Arch Otolaryngol 1931; 13:386-422.

5. Ramadier J. Exploration de la pointe du rocher par la voie du canal carotidien. Ann d'Oto-Laryngol 1933; 4:422.

6. Kopetzky SJ, Almour R. The suppuration of the petrous pyramid: pathology, symptomatology and surgical treatment. III. Surgical therapy. Ann Otol Rhinol Laryngol 1931; 40:396-414.

7. Lindsay JR. Labyrinthine dropsy and Ménière's disease. Arch Otolaryngol 1942; 35:853-67.

8. Hallpike CS, Cairns H. Observations on the pathology of Ménière's syndrome. Proc R Soc Med 1938; 31:1317-36.

9. Yamakawa K. Über die pathologische Veränderung bei einem Meniere-Kranken. J Otorhinolaryngol Soc Jap 1938; 44: 2310-2.

10. Lindsay JR. Effect of obliteration of the endolymphatic sac and duct in the monkey. Arch Otolaryngol 1947; 45:1-13.

11. Lindsay JR, Schuknecht HF, Neff WD, Kimura RS. Obliteration of the endolymphatic sac and the cochlear aqueduct. Ann Otol Rhinol Laryngol 1952; 61:697-716.

12. Lindsay JR, Neff WD, Schuknecht HF, Perlman HB. Obliteration of the ductus endolymphaticus and their accompanying venous channels. Acta Otolaryngol (Stockh) 1953; 43: 176-89.

13. Lindsay JR. Nonsecreting cysts of the maxillary sinus mucosa. Laryngoscope 1942; 52:84-100.

14. Lindsay JR, Templeton FE, Rothman S. Lesions of the esophagus in generalized progressive scleroderma. JAMA 1943; 123:745-50.

15. Brunschwig A, Lindsay JR. Further experiences with panlaryngectomy for advanced carcinoma of the larynx. Surg Gynecol Obstet 1946; 83:639-42.

16. Sourdille H. New technique in the surgical treatment of severe and progressive deafness from otosclerosis. Bull NY Acad Med 1937; 13:673-91.

17. Lempert J. Improvement of hearing in cases of otosclerosis. A new, one stage surgical technic. Arch Otolaryngol 1938; 28: 42-97.

18. Lindsay JR. Histologic observations on the healing of labyrinthine fistulas in monkeys. Arch Otolaryngol 1946; 43: 37-48.

19. Lindsay JR. Pathology of vertigo arising from the peripheral vestibular apparatus. Ann Otol Rhinol Laryngol 1947; 56: 541-56.

20. Lindsay JR. Postural vertigo and positional nystagmus. Ann Otol Rhinol Laryngol 1951; 60:1134-52.

21. Proctor B, Lindsay JR. Tuberculosis of the ear. Arch Otolaryngol 1942; 35:221-49.

22. Proctor B, Lindsay JR, Gonne WS. Sequestration of the osseous labyrinth. Arch Otolaryngol 1943; 37:819-30.

23. Lindsay JR, Harrison RS. The pathology of rubella deafness. J Laryngol Otol 1954; 68:461-4.

24. Lindsay JR, Hemenway WG. Postural vertigo due to unilateral sudden partial loss of vestibular function. Ann Otol Rhinol Laryngol 1956; 65:692-706.

25. Lindsay JR, von Schulthess G. An unusual case of labyrinthine hydrops. Acta Otolaryngol (Stockh) 1958; 49:315-24.

26. Lindsay JR, Davey PR, Ward PH. Inner ear pathology in deafness due to mumps. Ann Otol Rhinol Laryngol 1960; 69: 918-35.

27. Ward PH, Cannon D, Lindsay JR. The vestibular system in multiple sclerosis. A clinical-histopathological study. Laryngoscope 1965; 75:1031-47.

28. Ward PH, Lindsay JR, Warner NE. Cytomegalic inclusion disease affecting the temporal bone. Laryngoscope 1965; 75: 628-38.

29. Lindsay JR, Proctor LR, Work WP. Histopathologic inner ear changes in deafness due to neomycin in a human. Laryngoscope 1960; 70:382-92.

30. Fredrickson JM, Griffith AW, Lindsay JR. Transverse fracture of the temporal bone. A clinical and histopathological study. Arch Otolaryngol 1963; 78:770-84.

31. Lindsay JR, Beal DD. Sensorineural deafness in otosclerosis. Observations on histopathology. Ann Otol Rhinol Laryngol 1966; 75:436-57.

32. Beal DD, Lindsay JR, Ward PH. Radiation-induced carcinoma of the mastoid. Arch Otolaryngol 1965; 81:9-16.

33. Beal DD, Davey PR, Lindsay JR. Inner ear pathology of congenital deafness. Arch Otolaryngol 1967; 85:134-42.

34. Lindsay JR, Kohut RI, Sciarra PA. Menière's disease: pathology and manifestations. Ann Otol Rhinol Laryngol 1967; 76:5-22.

35. Lindsay JR, Lehman RH. Histopathology of the temporal bone in advanced Paget's disease. Laryngoscope 1969; 79:213-27.

36. Valvassori GE, Naunton RF, Lindsay JR. Inner ear anomalies: clinical and histopathological considerations. Ann Otol Rhinol Laryngol 1969; 78:929-38.

37. Cohn AM, Sataloff J, Lindsay JR. Histiocytosis X (Letterer-Siwe disease) with involvement of the inner ear. Arch Otolaryngol 1970; 91:24-9.

38. Lindsay JR, Zajtchuk J. Concussion of the inner ear. Ann Otol Rhinol Laryngol 1970; 79:699-709.

39. Zajtchuk JT, Matz GJ, Lindsay JR. Temporal bone pathology in herpes oticus. Ann Otol Rhinol Laryngol 1972; 81: 331-8.

40. Lindsay JR, Black FO, Donnelly WH Jr. Acrocephalosyndactyly (Apert's syndrome): temporal bone findings. Ann Otol Rhinol Laryngol 1975; 84:174-8.

41. Suga F, Lindsay JR. Histopathological observations of presbycusis. Ann Otol Rhinol Laryngol 1976; 85:169-84.

42. Suga F, Lindsay JR. Inner ear degeneration in acoustic neurinoma. Ann Otol Rhinol Laryngol 1976; 85:343-58.

43. Hinojosa R, Lindsay JR. Inner ear degeneration in Reye's syndrome. Arch Otolaryngol 1977; 103:634-40.

44. Hinojosa R, Lindsay JR. Profound deafness. Associated sensory and neural degeneration. Arch Otolaryngol 1980; 106: 193-209.

45. Lindsay JR, Hinojosa R. Ear anomalies associated with renal dysplasia and immunodeficiency disease. Ann Otol Rhinol Laryngol 1978; 87:10-7.

46. Hipskind MM, Lindsay JR, Valvassori GE. Recurrent meningitis and labyrinthine gusher, related to congenital defects of the labyrinthine capsule and stapes footplate. Laryngoscope 1976; 86:682-9.

47. Lindsay JR, Schuknecht HF. Intracranial complications in otolaryngology. Arch Otolaryngol 1948; 48:597-608.

48. Schuknecht HF, Lindsay JR. Benign cysts of the paranasal sinuses. Arch Otolaryngol 1949; 49:609-30.

OTONEUROLOGY

JOHN M. FREDRICKSON, MD

John Lindsay was the dean of otoneurology. He had no peer in his sagacious blending of research with clinical observations. Although he was known primarily for his expertise in otoneurology and temporal bone histopathology, which Dr. Schuknecht has just reviewed (this supplement), he also contributed significantly to auditory research.

In 1936, an investigation with Drs. Kobrak and Perlman demonstrated for the first time[1] that it was possible to compare the curve of hearing and the curve of the stapedial muscle reflex (see Figure). The relationship between the two curves led them to conclude that a normal stapedial reflex may be taken as an indicator of relatively good hearing, and that the stapedial reflex could be used in an objective test of hearing.

Further animal experiments in 1936 demonstrated that the movement of perilymph in the cochlea was diminished or abolished when the round window was plugged,[2] and that this movement was reduced by impairment of the ossicular chain. The movement of the round window was noted to be opposite to that of the stapes during stimulation. This was presumed to produce a synergistic effect on perilymphatic movement, resulting in increased stimulation of the organ of Corti. The investigators concluded from clinical observations that the stapedial reflex is a normal physiologic phenomenon acting primarily as a protective mechanism and bearing a definite relationship to the hearing sensation.

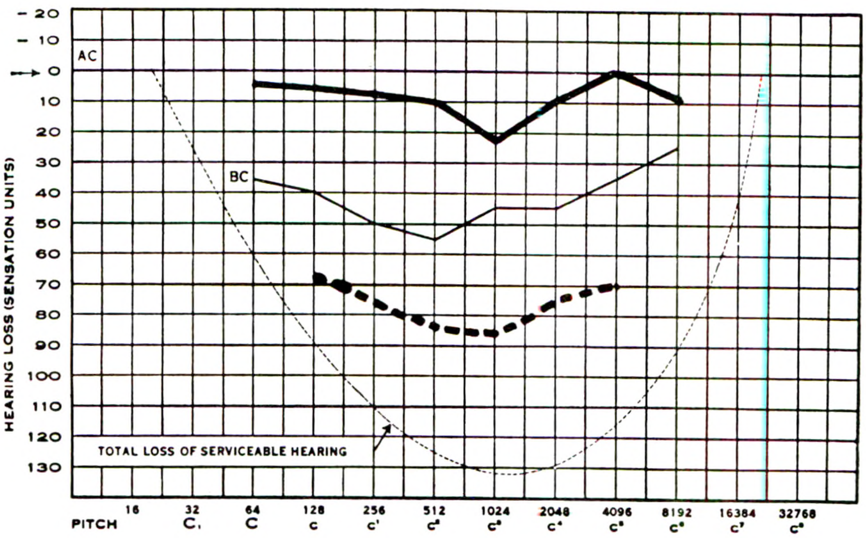
Twenty-two years later, in 1958, John Lindsay, working with Drs. César Fernández and G. W. Allen, tested the theory that the transformer action of the ossicular chain is a sufficient but not a necessary condition for normal or near-normal hearing.[3] Cochlear microphonic and nerve action potential measurements were made under a variety of conditions, including disarticulation of the incudostapedial joint and mechanical fixation of the stapes. The expected threshold shifts of these responses were determined and remeasured after fenestration of the oval window. The results indicated that the fenestra ovalis did not restore the normal reference point of an inner ear response; therefore, their theory could not be supported.

A paper entitled "The Utriculo-Endolymphatic Valve,"[4] which John Lindsay coauthored with Dr. Henry Perlman in 1936, was a classic example of a simple anatomic observation which, combined with clinical knowledge, led to some interesting conclusions. They assumed that this valve had some specific physiologic function. The question they posed was why dynamic waves of high amplitude entering the vestibule do not cause any disturbance of the vestibular receptors. After a careful review of temporal bone sections, they thought that the utriculoendolymphatic valve might play some role in preventing perturbation of the end-organ under such conditions. They suggested that, by using models and animal experiments, one could determine whether the utriculoendolymphatic valve insulated the utricular contents from pressure changes.

In the early 1940s, there was a popular theory to the effect that the vestibulovasomotor reaction, which is a part of the syndrome of motion sickness, was localized in a certain portion of the labyrinthine receptors. Dr. Lindsay demonstrated in animal studies in 1945[5] that destruction of portions of the maculae or semicircular canal ampullae did not result in disappearance of the vasomotor reaction, and that complete destruction of the end-organ was required to prevent the reaction. Thus, he could not support the concept that there was a specific portion of the vestibular end-organ that was responsible for this part of the motion sickness syndrome.

In a classic paper on postural vertigo and positional nystagmus,[6] Dr. Lindsay carefully described methods of examining patients for positional nystagmus, classifications of this disorder, and its clinical importance, pathogenesis, and treatment. Research which he carried out with Dr. Fernández in 1960 indicated that the nodulus of the cerebellum acts as an inhibitor of the vestibular system.[7] They reported that postural nystagmus produced by ablation of the nodulus could be eliminated by bilateral labyrinthectomy, which indicated that signals from the vestibular end-organ are necessary for the production of the nystagmus. That paper is particularly interesting because advances in the diagnosis of the central vestibular syndrome these days are based on the inhibitory influence of the cerebellum on the activity of the vestibular reflex arc.

Hydrops of the labyrinth was one of Dr. Lindsay's particular interests, and he wrote several articles on that topic.[8-11] Day and Lindsay[8] passed a fine needle through the horizontal semicircular canal in order to destroy the ampullae with a coagulating current. It became clear histopathologically that the coagulation procedure used could destroy



Comparison of curve of hearing and curve of stapedial muscle reflex. Upper line represents curve for hearing of left ear by air conduction (AC), tested with 2-A audiometer. Heavy dotted line indicates threshold of contraction of right stapedius tendon, with telephone membrane of audiometer on left ear. BC - Bone conduction.

some portions of the end-organ while sparing others. It was this case to which Dr. Lindsay was able to refer later, when ultrasound therapy for Menière's disorder became popular. He eventually concluded that the use of ultrasound in the case of hydrops was no guarantee that future attacks of vertigo would be prevented, since, frequently, the entire vestibular end-organ was not destroyed.

In "Some Experimental Observations Bearing On Meniere's Disease,"[12] in 1953, Dr. Lindsay concluded from temporal bone studies in man and animals that there were certain essential differences between the classic Menière's disease and the hydrops found in disorders such as serous labyrinthitis, diseases of the labyrinthine capsule, leukemia, or experimentally induced irritative reactions of the perilymphatic space. In hydrops caused by inflammatory and irritative reactions, the significant and early lesions consisted of nerve and end-organ degeneration, with hydrops a minor component. In Menière's disorder, he found that, even if the hydrops was far advanced, the nerve fibers and ganglion cells, as well as the perilymphatic space in the bony labyrinthine capsule, may remain normal (see Schuknecht, Fig. 3, p. 14, this supplement).

The results that John Lindsay obtained in using ultrasound therapy for the control of vertigo due to Menière's disease were consistently favorable, as he reported in an article in 1959.[13] All patients retained their hearing, and there were no cases of facial palsy. Thus, in the small number of cases which he studied, he felt justified in using ultrasound therapy in preference to other methods of labyrinthine destruction so that residual hearing could be preserved.

When I was a resident a few years later, Dr. Lindsay asked me to review the cases treated with ultrasound. He was concerned because some of the patients were returning with episodic attacks of vertigo. For me, this was an excellent lesson in withholding a final decision on therapeutic efficacy until a long-term follow-up was completed. Moreover, it was a sterling example of Dr. Lindsay's professional integrity, since his eventual findings refuted his earlier conclusions.

A particularly interesting article in 1965 described the intermittent attacks of vertigo associated with multiple sclerosis,[14] which was known at times to mimic cases of Menière's disease or acoustic neuroma. It had been assumed that the lesions of multiple sclerosis were restricted to the central nervous system, but there was no histopathologic proof of that. Microscopic study of the temporal bones and central nervous system from such a patient demonstrated the confinement of the lesions to the central nervous system.

Dr. Lindsay's retirement did not interrupt his research productivity. Almost 60 journal articles and book chapters were published after he had officially retired. This is a remarkable achievement, especially when one considers the quality of the contributions.

Even though Dr. Lindsay spent his entire professional career an an academic otolaryngologist at the University of Chicago, he was not a cloistered scientist. His philosophy and activities were truly international in scope. He knew that science belongs to everyone, and his great legacy was to pass that attitude on to so many of us. It is a legacy which we should carry forward with pride and, in turn, pass on to a succession of students so that the concept will continue to thrive.

REFERENCES

1. Lindsay JR, Kobrak H, Perlman HB. Relation of the stapedius reflex to hearing sensation in man. Arch Otolaryngol 1936; 23:671-8.

2. Kobrak H, Lindsay JR, Perlman HB. Acoustic stimulation of inner ear by application of sound into cavity of middle ear. Arch Otolaryngol 1936; 23:39-47.

3. Fernández C, Allen GW, Lindsay JR. Experimental studies in fixation of the stapes and fenestra ovalis. Laryngoscope 1958; 68:1881-907.

4. Perlman HB, Lindsay JR. The utriculo-endolymphatic valve. Arch Otolaryngol 1936; 24:68-75.

5. Lindsay JR, Oppenheimer MJ, Wycis HT, Spiegel EA. Receptor apparatus of the vestibulovasomotor reaction. Arch Otolaryngol 1945; 42:257-66.

6. Lindsay JR. Postural vertigo and positional nystagmus. Ann Otol Rhinol Laryngol 1951; 60:1134-52.

7. Fernández C, Alzate R, Lindsay JR. Experimental observations on postural nystagmus. II. Lesions of the nodulus. Ann Otol Rhinol Laryngol 1960; 69:94-114.

8. Day KM, Lindsay JR. Hydrops of the labyrinth. Case report. Coagulation operation, clinical course and histopathology. Laryngoscope 1949; 59:213-27.

9. Lindsay JR, von Schulthess G. An unusual case of labyrinthine hydrops. Acta Otolaryngol (Stockh) 1958; 49:315-24.

10. Lindsay JR. Hydrops of the labyrinth. Arch Otolaryngol 1960; 71:500-10.

11. Kohut RI, Lindsay JR. Pathologic changes in idiopathic labyrinthine hydrops. Acta Otolaryngol (Stockh) 1972; 73: 402-15.

12. Lindsay JR. Some experimental observations bearing on Meniere's disease. Trans Am Acad Ophthalmol Otolaryngol 1953; 57:27-34.

13. Ironside WMS, Lindsay JR. Ultrasonic therapy for relief of vertigo due to Meniere's disease. Laryngoscope 1959; 69:899-913.

14. Ward PH, Cannon D, Lindsay JR. The vestibular system in multiple sclerosis. A clinical-histopathological study. Laryngoscope 1965; 75:1031-47.

THE CLINICAL RESEARCH OF JOHN LINDSAY

ROBERT I. KOHUT, MD

We know all the admirable things about Dr. Lindsay; but those who worked with him also know that he was never without a good joke up his sleeve. He was my constant advisor and my prophet. Therefore, I phoned him when I was considering my move to North Carolina. I was thinking in terms of academic purposes and the like when I asked him, "Dr. Lindsay, do you think that I should make this move?" There was a moment of silence, and then he asked, "Bob, are you still smoking?" I said, "Yes, sir, I am." And he replied, "Well, you'll be closer to the source."

Among his numerous publications, Dr. Lindsay's clinical studies focused on three main areas. The first comprised nasal and sinus problems; the second, esophageal lesions; and the third, neoplasms, including those of the larynx, the sinus, and the temporal bone. Dr. Lindsay's first paper, published in 1933, presented a cellular analysis of nasal secretions.[1] He stated that normal secretions showed no cellularity, whereas many cells were present in the secretions of patients with chronic sinusitis or acute rhinosinusitis. Allergic rhinitis was diagnosed if skin tests were positive in a patient whose nasal smear contained eosinophils. The term "vasomotor rhinitis" was used for those patients in whom this eosinophilia was present and yet there was no demonstrable allergy by skin test.

In 1934, John Lindsay published a rather extensive study entitled "Cytology of Nasal Polypi,"[2] which seemed a logical extension of the earlier study on nasal smears. His goal in this second study was to correlate clinical and histocytologic findings in order to determine whether definite etiologic factors could be found. He concluded that skin tests in patients with type A polypi (with numerous eosinophils) were negative because the tests were inaccurate. His second conclusion was that, in contrast to patients with type A, patients with type B polypi, which presumably were nonallergenic and were the secondary effects of infection, seemed to respond well to operative treatment. In "Chronic Sinusitis in Children,"[3] Dr. Lindsay made some general observations: children with sinusitis and eosinophilia of the nasal secretions need less vigorous management than do those without such eosinophilia; and children with sinusitis and bronchitis or early bronchiectasis are most urgently in need of vigorous treatment.

As his candidate's thesis for the Triological Society, in 1941, Dr. Lindsay published "Nonsecreting Cysts of the Maxillary Sinus Mucosa."[4] Eight years later, he and his student, Harold Schuknecht, reported on a detailed study of benign cysts of the paranasal sinuses.[5] They presented clinical evidence that a nonsecreting cyst may act as a focus of infection. The description of details of mucocele and dental cyst formation remains extremely accurate and serves today as a useful point of reference.

John Lindsay's interest in diseases of the esophagus became apparent in 1941, with the publication of a paper entitled "The Early Diagnosis of Carcinoma of the Esophagus,"[6] a clinical problem that certainly remains with us still. In this paper, Dr. Lindsay identified carcinoma of the esophagus as the cause of some 2% to 8% of all tumor deaths. He urged early and thorough diagnostic studies by radiographic and endoscopic means. His enthusiasm is accounted for by his recognition of the strides being made in thoracic surgery at the time, so that resection was feasible in suitable patients. Until these surgical efforts were made, the disease had been 100% fatal, even with radiation therapy. Dr. Lindsay indicated that most esophagoscopies can be performed under local anesthesia, with three considerations to be kept in mind: the adequacy and thoroughness of the examination, the safety of the patient, and the discomfort caused.

Two years later, the classic paper, "Lesions of the Esophagus in Generalized Progressive Scleroderma,"[7] was published. After giving a descriptive review of the characteristics of scleroderma and noting that almost all patients had early symptoms of heartburn which were later masked by the intensity of the skin and joint problems, Dr. Lindsay and his coauthors, one of whom was the famous dermatologist, Dr. Stephen Rothman, indicated that little attention had been paid to patients having this disorder. In all of the studies carried out until that time, only one patient with scleroderma had had an esophagoscopy. The authors reviewed their series of patients and reported the radiologic, endoscopic, and histologic findings. They identified the loss of peristalsis, as well as the relaxation and dilatation that developed in the lower two thirds of the esophagus.

A subsequent paper, entitled "Esophageal Lesions in Diffuse Scleroderma,"[8] described further experience and autopsy material. Dr. Lindsay reached two distinct conclusions in this continuation of his 1943 paper: first, that general anesthesia was safer than local anesthesia for esophagoscopy in

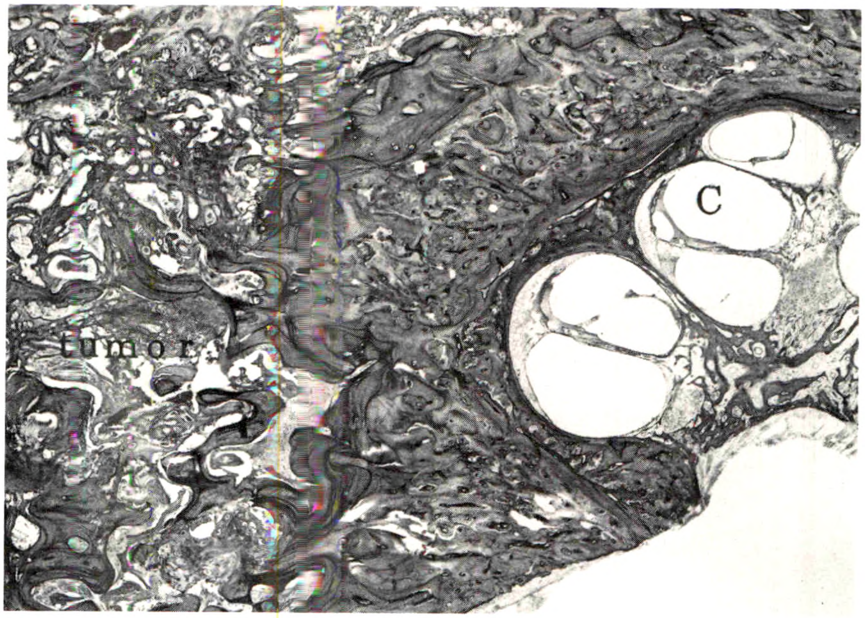


Fig. 1. Section of temporal bone of patient who had been a radium dial painter, showing cochlea (C) and normal otic capsule. Apical region of temporal bone has been invaded by tumor, but otic capsule is tumor-free.

patients with a fibrosed esophagus; and second, that the esophageal stenosis occurred not in the region above the phrenic ampulla, but at the esophagogastric junction.

In 1944, Drs. Lindsay, Morgan, and Wepman reported the sequence of events in esophageal speech in "The Cricopharyngeus Muscle in Esophageal Speech."[9] They used unique timing methods to study the function of the cricopharyngeus fluoroscopically and with spot films so that the 1/20-second and 1/30-second exposures used gave revealing images. Radiography showed differences in cricopharyngeal function between patients who had good voice and those who had poor esophageal speech. The investigators must have persevered in this study; how easily it could have been done with today's equipment!

Dr. Lindsay's last paper related to the esophagus and deglutition, published in 1955, was entitled "Functional Disturbances of the Upper Swallowing Mechanism."[10] In it, he developed an approach to the evaluation of disorders of the physiologic mechanism of swallowing disorders, stating that such disorders are of three types, muscular, neural, and psychogenic, all without any alteration of structure. The psychogenic type remained a diagnosis of exclusion. However, he suggested the need for a test for increased tone or spasm, lest an inappropriate psychogenic diagnosis be made. It seems that we have this test today in manometry.

Dr. Lindsay's interest in neoplasia became apparent in 1946. He was coauthor with Dr. Brunschwig of the paper "Further Experiences with Panlaryngectomy for Advanced Carcinoma of the Larynx,"[11] in which they related their experience with wide resection. This procedure included a "modified neck" dissection consisting of the removal of the sternocleidomastoid muscle and one jugular vein, along with the strap muscles and larynx, with tracheal exteriorization, as is presently done. There seems to be something familiar here almost 40 years later. The approach to a modified neck dissection, the evaluation of prophylactic antibiotics, and the development of an artificial larynx were all contained within this article published in 1946.

In 1955, Drs. Ironside and Lindsay reported on "Carcinoma of the Larynx, Classification and Results of Treatment."[12] The authors welcomed the classification described by the International Committee for Stage-grouping in Cancer and for the Presentation of the Results of Treatment of Cancer. After evaluating their results by that classification, they came to the following conclusions: supraglottic carcinoma requires surgical treatment; for glottic carcinoma in stages 1 and 2, radiation therapy should be the initial treatment, since surgical salvage of radiation failures had resulted in a cure rate similar to that when the initial therapy was surgery. In an extension of the 1955 study, "Carcinoma of the Larynx. Results Obtained by Surgery and External Radiation in Ninety-three Cases,"[13] Lindsay, Ironside, and their coauthors concluded that supraglottic and subglottic carcinomas, except those in stage 1, required surgical resection, including bilateral neck dissection.

In the same year, 1959, Drs. Hemenway and Lindsay published "Malignancies of the Paranasal Sinuses,"[14] in which they reviewed results in 62 cases. Distinct differences in outcome were identified for treatment of sarcomas and carcinomas. With irradiation, the cure rate was 80% for sarcomas and 0% for carcinomas, even with surgical salvage. After they instituted radical surgery, alone or followed by irradiation, they obtained a 50% cure rate. The surgical techniques used were those described by Schuknecht and Tabb. Thus, we again hear the name of Schuknecht, who determined the appropriate surgical treatment for carcinoma of the

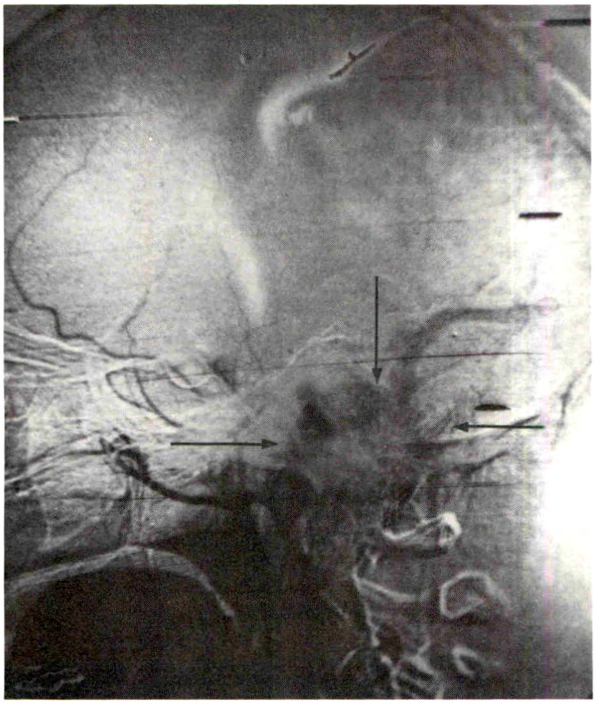


Fig. 2. Subtraction angiogram demonstrating size of tumor. Feathery vasculature of large tumor is outlined by arrows.

maxilla, a treatment that changed the survival rate from 0% to 55%.

Dr. Lindsay and his colleagues published two papers in 1965 on tumors of the temporal bone. The first, by Drs. David Beal, John Lindsay, and Paul Ward, was entitled "Radiation-Induced Carcinoma of the Mastoid."[15] Here they reported the temporal bone findings in two radium dial painters who died of carcinoma of the mastoid (Fig. 1). They reviewed the dynamics of radium poisoning and described the histopathologic changes, not confining their comments to individuals who worked with radium, but including patients who received radium water, a fashionable form of treatment in the third and fourth decades of this century.

In "Glomus Jugulare Tumors. New Techniques for Determining Operability,"[16] Dr. Lindsay and I reviewed the cases seen at the University of Chicago Clinics. We reviewed the history of the glomus body, tumors of that body, and the development of diagnostic and treatment methods, and we described histologic findings in temporal bones, illustrating the routes of tumor invasion and the usefulness of polytomography and subtraction angiography in the evaluation of the lesions (Fig. 2). The two diagnostic radiologic methods were considered useful in the determination of resectability.

It is clear, when one reviews the other research activities of Dr. John Lindsay, that his interests were as varied as the broad field of otolaryngology. It is to be hoped that some of the questions posed by his studies will be recognized by young investigators and used as a point of reference for new research that will further add to our fund of knowledge.

REFERENCES

1. Lindsay JR, Walsh TE. Nasal secretions: the value of cytologic examination to the rhinologist. Arch Otolaryngol 1933; 17: 783-6.

2. Walsh TE, Lindsay JR. Cytology of nasal polypi. Arch Otolaryngol 1934; 20:649-58.

3. Lindsay JR. Chronic sinusitis in children. Illinois Med J 1937; April:1-9.

4. Lindsay JR. Nonsecreting cysts of the maxillary sinus mucosa. Laryngoscope 1942; 52:84-100.

5. Schuknecht HF, Lindsay JR. Benign cysts of the paranasal sinuses. Arch Otolaryngol 1949; 49:609-30.

6. Lindsay JR. The early diagnosis of carcinoma of the esophagus. Ann Otol Rhinol Laryngol 1941; 50:675-80.

7. Lindsay JR, Templeton FE, Rothman S. Lesions of the esophagus in generalized progressive scleroderma. JAMA 1943; 123:745-50.

8. Lindsay JR. Esophageal lesions in diffuse scleroderma. Laryngoscope 1949; 59:83-112.

9. Lindsay JR, Morgan RH, Wepman JM. The cricopharyngeus muscle in esophageal speech. Laryngoscope 1944; 54:55-65.

10. Lindsay JR. Functional disturbances of the upper swallowing mechanism. Ann Otol Rhinol Laryngol 1955; 64:766-76.

11. Brunschwig A, Lindsay JR. Further experiences with panlaryngectomy for advanced carcinoma of the larynx. Surg Gynecol Obstet 1946; 83:639-42.

12. Lindsay JR, Ironside WMS. Carcinoma of the larynx, classification and results of treatment. Laryngoscope 1955; 65:1117-28.

13. Ironside WMS, Carpender JWJ, Roedal R, Lindsay JR. Carcinoma of the larynx. Results obtained by surgery and external radiation in ninety-three cases. JAMA 1959; 169:783-6.

14. Hemenway WG, Lindsay JR. Malignancies of the paranasal sinuses. Arch Otolaryngol 1959; 70:61-4.

15. Beal DD, Lindsay JR, Ward PH. Radiation-induced carcinoma of the mastoid. Arch Otolaryngol 1965; 81:9-16.

16. Kohut RI, Lindsay JR. Glomus jugulare tumors. New techniques for determining operability. Laryngoscope 1965; 75:750-62.

PIONEERS IN RESEARCH IN OTOLARYNGOLOGY AT THE UNIVERSITY OF CHICAGO

CÉSAR FERNÁNDEZ, MD

The qualifications of John Lindsay as a clinician, administrator, teacher, and researcher made him an ideal chairman. As a chairman of sound judgment, he appointed to the staff, from the beginning of his career, a number of otolaryngologists who contributed substantially to the explosive progress of the specialty, in both its clinical and basic science aspects, from the early 1930s to the present time. I would like to mention four of these pioneers: Theodore E. Walsh, Henry B. Perlman, Heinrich F. G. Kobrak, and Harold F. Schuknecht.

THEODORE E. WALSH (1900-1971)

Theodore E. Walsh was born on September 1, 1900, in Calcutta, India. He received an AB degree from King's College, Cambridge, in 1921. He then studied medicine at St. Thomas's Hospital in London, where he was awarded an LRCP (London) and an MRCS (England) in 1925. After an internship at the Royal Hampshire County Hospital, he was appointed as a medical officer to the Sarawak government in Borneo, where he practiced general surgery for two and one half years. Returning to England by way of the United States, he visited the Department of Surgery at the University of Chicago. Dr. Phemister, then chairman of the department, advised him that he should look over a position that was available in the Section of Otolaryngology, with the result that Dr. Lindsay appointed him an assistant resident in 1929. He remained in Chicago until 1940, when he accepted the chairmanship of the Department of Otolaryngology at Washington University in St. Louis.

From 1944 to 1971, Walsh served as editor of the *Laryngoscope*, maintaining the prestige brought to that journal by its founder, Dr. Max A. Goldstein. Walsh also edited the Transactions of the Triological Society with great distinction from 1946 to 1967. He remained at Washington University until his retirement in 1966, but continued his work and duties as professor emeritus until his death on April 29, 1971.

At the University of Chicago, in collaboration with John Lindsay, he studied the cytologic differentiation of nasal allergic secretions from those of bacterial origin, and also the histologic differences between polypi of allergic and infectious origin.[1,2] Together with Dr. Paul R. Cannon, of the Department of Pathology, he initiated a series of experiments on prevention of the common cold by means of immunization of the nasal mucosa and respiratory tract with local application of polyvalent vaccines.[3] His experiments were well designed and controlled; he was highly critical of his own results.

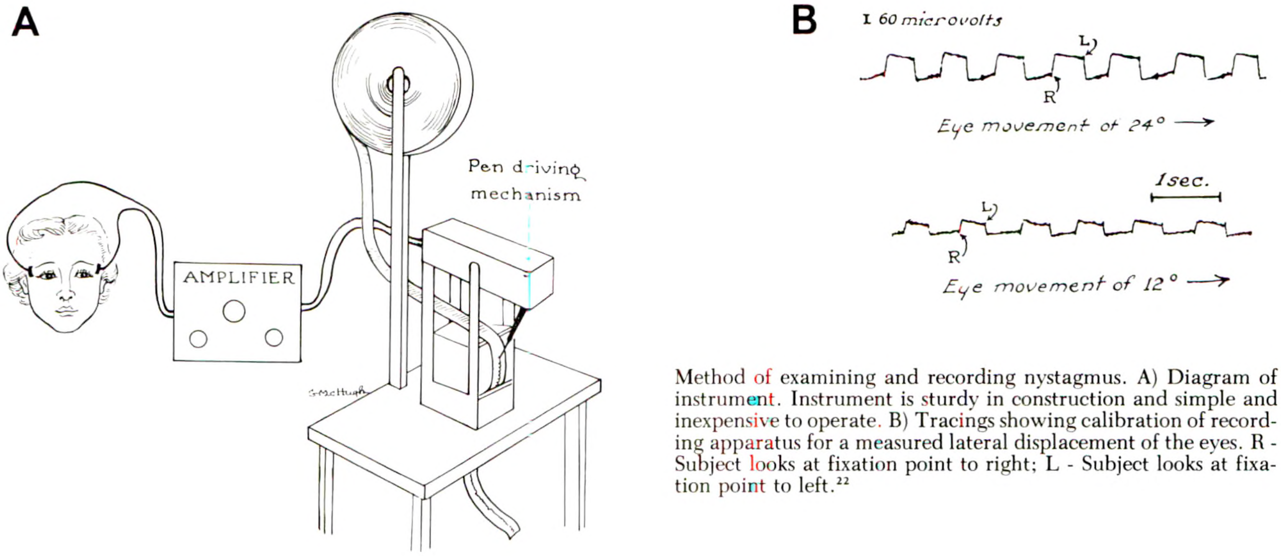
Theo was a skillful ear surgeon who turned his main research interest toward evaluation of hearing following surgical procedures on the ear, particularly fenestration operations, which were much in vogue in the early 1940s. At Washington University, he was associated with three scientists from the Central Institute for the Deaf, Drs. H. Davis, S. R. Silverman, and W. R. Thurlow, in this work. They formed a perfect team which established the standards for evaluation of hearing after procedures such as fenestration operations and stapes surgery.[4-10]

At Washington University, Theodore Walsh was an excellent chairman who followed, within the framework of his own personality, the model established at the University of Chicago by his teacher, John R. Lindsay.

HENRY B. PERLMAN (1901-)

Henry B. Perlman, born in Russia on July 15, 1901, received a BA degree from the University of Wisconsin and, in 1926, an MD degree from Rush Medical College. After an internship at Los Angeles General Hospital, he did general practice for four years in Belleville, Wisconsin. He entered a residency in otolaryngology at the University of Chicago in 1930 and joined the full-time faculty in 1933. He became a full professor in 1952 and professor emeritus in 1968.

Throughout his career, Henry Perlman made many contributions to our understanding of middle and inner ear function in health and disease. He provided new information on middle ear muscle reflexes,[11] on the dynamics of the ossicular chain,[12-14] on the utriculoendolymphatic valve,[15] on dysfunction of the eustachian tube,[16,17] and on inner ear disorders caused by acoustic trauma and fatigue,[18] Paget's disease,[19] and vitamin A deficiency.[20] In collaboration with Dr. T. J. Case, an electronics engineer in charge of the electroencephalography laboratory in Neurology, he measured the latency of the stapedial muscle reflex by recording action currents from the stapedius tendon in human subjects who had large perforations of the tympanic membrane.[21]



Method of examining and recording nystagmus. A) Diagram of instrument. Instrument is sturdy in construction and simple and inexpensive to operate. B) Tracings showing calibration of recording apparatus for a measured lateral displacement of the eyes. R - Subject looks at fixation point to right; L - Subject looks at fixation point to left.[22]

Perlman's interest in otoneurology led him to the problem of recording eye movements associated with diseases of the vestibular system; for this purpose, he again collaborated with Dr. Case. In the 1930s, the existence of the corneoretinal potential and its value as a means for studying eye movements were known. Using this information, the team of Perlman and Case built, for the first time, a simple, efficient, and inexpensive electronystagmograph with a time constant of 1 second.[22] A diagram of the instrument and the calibration procedure are illustrated in the Figure. The records they obtained were excellent, even by present-day standards. They explored and recorded eye movements in normal subjects and in patients with a variety of diseases.[23]

In the early 1950s, Perlman joined Dr. Robert Kimura in studying the circulation of the cochlea. Kimura, a skillful surgeon, was able to fenestrate the apex of the guinea pig cochlea, so that the blood vessels of the stria vascularis were visualized. By means of cinematography, Perlman and Kimura provided new information on cochlear blood flow affected by anoxia,[24] anaphylaxis,[24] hypothermia,[25] acoustic trauma,[26] and other experimental conditions. They found to their surprise that sympathetic stimulation did not change the blood circulation significantly.[24] Their reports on histopathologic changes associated with interruption of the arterial and venous blood supply of the inner ear are classic contributions that remain unsurpassed.[27-30]

HEINRICH F. G. KOBRAK (1905-1957)

Heinrich F. G. Kobrak was born in Berlin on March 19, 1905. He received an MD degree from the University of Munich in 1929, and carried on postgratuate work at Basel (1929), Münster (1930-1932), and Heidelberg (1933). After he immigrated to the United States, John Lindsay appointed him to the staff of the Otolaryngology Section at the University of Chicago in 1934. Three years later, he was awarded a PhD degree in physiology for work on the function of sound-conducting mechanisms of the middle ear. In 1954, he left the University of Chicago to become professor of otolaryngology at Wayne State University. He died on October 9, 1957, at his home in Clarkston, Michigan.

The development of research in the Section of Otolaryngology was greatly influenced by John Lindsay's appointment of Kobrak. The new ideas which he introduced on the biophysics of the middle ear muscles and ossicular chain led to a period of intense research in this field by the team composed of Kobrak, Lindsay, Perlman, and Case.

Kobrak measured the sensitivity of the reflex of the middle ear muscles as a function of frequency and, in collaboration with Lindsay and Perlman, confirmed that the acoustic reflex is bilateral no matter which ear is stimulated. In addition, he measured the latency of the reflex in man and animals,[31] as well as changes in the reflex as a function of middle ear pressure.[32,33] He demonstrated the amplitude asymmetry of the tympanic membrane when it was subjected to a wide range of static air pressures, but found that, within physiologic limits, the displacement was linear.[34] By his measurements of the natural frequency of the ossicular chain, he provided useful information on the vibratory pattern of the ossicles.[31] He was an expert in cinematography, which he used for the study of movements of the ossicular chain and for teaching purposes.

HAROLD F. SCHUKNECHT (1917-)

Harold F. Schuknecht was born on February 10, 1917, in Chancellor, South Dakota. His graduation from Rush Medical College in 1940 was followed by an internship at Mercy Hospital in Des Moines. After World War II, he entered the residency program in otolaryngology at the University of Chicago

(1946-1949). He served as a member of the staff until 1953, when he became chairman of otolaryngology at Henry Ford Hospital in Detroit, a post he held until 1961. Thereafter, he took on the position of chairman and professor of otology at Harvard University.

At the University of Chicago, he was influenced by the exciting research atmosphere created by Lindsay, Perlman, and Kobrak. His own research interest was directed toward the study of frequency localization in the cochlea. Audiograms were obtained by the avoidance-conditioning technique practiced by Dr. W. Dewey Neff. In collaboration with Lindsay, Perlman, and Neff and his students, Schuknecht carried out a series of animal experiments which provided new information on frequency representation along the cochlea.[35-40] He standardized the method of graphic reconstruction of the histopathologic findings in auditory sense organs and nerves and their associated auditory function.[41] The method is still widely used in animals and also in man.

Schuknecht's other contributions to otolaryngology are numerous, but here I will mention only two. He and his collaborators were the first to provide histochemical evidence that the fibers of the efferent system of the cochlea are cholinergic. The implication of this finding is that the transmitter of the efferent system at the sensory epithelium is acetylcholine.[42] Second, because of the early influence and teaching of Lindsay and other pioneers at the University of Chicago, Schuknecht developed into a prolific researcher on the pathology of the human temporal bone.[43] Throughout the years, he has made many contributions in this field and postulated many new concepts.

CONCLUSION

These otolaryngologists, judiciously selected and trained by John R. Lindsay, devoted their undivided professional attention to the early development of our section at the University of Chicago. Under the leadership of Lindsay, they recognized as a desirable model for a teaching institution the combination of clinical practice with teaching and research. They approached both basic and clinical research with honesty and integrity. Each as an individual with his own research interests, and all together as a group, reached a state of eminence and distinction which has had a profound and permanent impact on the progress of otolaryngology in this country and abroad.

REFERENCES

1. Lindsay JR, Walsh TE. Nasal secretions: the value of cytologic examination to the rhinologist. Arch Otolaryngol 1933; 17:783-6.

2. Walsh TE, Lindsay JR. Cytology of nasal polypi. Arch Otolaryngol 1934; 20:649-58.

3. Walsh TE, Cannon PR. Immunization of the upper respiratory tract. Arch Otolaryngol 1934; 20:820-36.

4. Walsh TE, Silverman SR. Diagnosis and evaluation of fenestration. Laryngoscope 1946; 56:536-55.

5. Thurlow WR, Silverman SR, Davis H, Walsh TE. A statistical study of auditory tests in relation to the fenestration operation. Laryngoscope 1948; 58:43-66.

6. Silverman SR, Thurlow WR, Walsh TE, Davis H. Improvement in the social adequacy of hearing following the fenestration operation. Laryngoscope 1948; 58:607-31.

7. Thurlow WR, Davis H, Silverman SR, Walsh TE. Further statistical study of auditory tests in relation to the fenestration operation. Laryngoscope 1949; 59:113-29.

8. Davis H, Walsh TE. The limits of improvement of hearing following the fenestration operation. Laryngoscope 1950; 60:273-95.

9. Davis H, Walsh TE, Eldert E. Closure and revision following the fenestration operation. Laryngoscope 1950; 60: 1181-9.

10. Thurlow WR, Davis H, Walsh TE, Eldert E. A third statistical study of auditory tests in relation to the fenestration operation. Laryngoscope 1951; 61:24-37.

11. Lindsay JR, Kobrak H, Perlman HB. Relation of the stapedius reflex to hearing sensation in man. Arch Otolaryngol 1936; 23:671-8.

12. Perlman HB. Physics of conduction apparatus. Laryngoscope 1945; 55:337-48.

13. Perlman HB. Reaction of the human conduction mechanism to blast. Laryngoscope 1945; 55:427-43.

14. Perlman HB. Some physical properties of the conduction apparatus. Ann Otol Rhinol Laryngol 1947; 56:334-46.

15. Perlman HB, Lindsay JR. The utriculo-endolymphatic valve. Arch Otolaryngol 1936; 24:68-75.

16. Perlman HB. The eustachian tube: abnormal patency and normal physiological state. Arch Otolaryngol 1939; 30:212-38.

17. Perlman HB. Quantitative tubal function. Arch Otolaryngol 1943; 38:453-65.

18. Perlman HB. Acoustic trauma in man. Clinical and experimental studies. Arch Otolaryngol 1941; 34:429-52.

19. Lindsay JR, Perlman HB. Paget's disease and deafness. Arch Otolaryngol 1936; 23:580-7.

20. Perlman HB, Willard J. The ear in experimental vitamin A deficiency. Ann Otol Rhinol Laryngol 1941; 50:349-62.

21. Perlman HB, Case TJ. Latent period of the crossed stapedius reflex in man. Ann Otol Rhinol Laryngol 1939; 48:663-75.

22. Perlman HB, Case TJ. Nystagmus: some observations based on an electrical method for recording eye movements. Laryngoscope 1939; 49:217-28.

23. Perlman HB, Case TJ. Mechanisms of ocular movement in man. Influence of vestibular apparatus. Arch Otolaryngol 1944; 40:457-67.

24. Perlman HB, Kimura R. Observations on the living blood vessels of the cochlea. Ann Otol Rhinol Laryngol 1955; 64:1176-92.

25. Perlman HB, Kimura R, Butler RA. Cochlear blood flow during hypothermia. Ann Otol Rhinol Laryngol 1959; 68:803-15.

26. Perlman HB, Kimura R. Cochlear blood flow in acoustic trauma. Acta Otolaryngol (Stockh) 1962; 54:99-110.

27. Kimura R, Perlman HB. Extensive venous obstruction of the labyrinth. A. Cochlear changes. Ann Otol Rhinol Laryngol 1956; 65:332-50.

28. Kimura R, Perlman HB. Extensive venous obstruction of the labyrinth. B. Vestibular changes. Ann Otol Rhinol Laryngol 1956; 65:620-38.

29. Perlman HB, Kimura R. Experimental obstruction of the venous drainage and arterial supply of the inner ear. Ann Otol Rhinol Laryngol 1957; 66:537-46.

30. Kimura R, Perlman HB. Arterial obstruction of the labyrinth. Part I. Cochlear changes. Part II. Vestibular changes. Ann Otol Rhinol Laryngol 1958; 67:5-40.

31. Kobrak HG. The middle ear. Chicago: University of Chicago Press, 1959.

32. Kobrak H. Influence of middle ear on labyrinthine pressure. Arch Otolaryngol 1935; 21:547-60.

33. Kobrak H, Lindsay JR, Perlman HB. Acoustic stimulation of inner ear by application of sound into cavity of middle ear. Arch Otolaryngol 1936; 23:39-47.

34. Kobrak H. Construction material of the sound conduction system of the human ear. J Acoust Soc Am 1948; 20:125-30.

35. Schuknecht HF, Neff WD, Perlman HB. An experimental study of auditory damage following blows to the head. Ann Otol Rhinol Laryngol 1951; 60:273-89.

36. Schuknecht HF, Neff WD. Hearing losses after apical lesions in the cochlea. Arch Otolaryngol (Stockh) 1952; 42:263-74.

37. Schuknecht HF, Sutton S. Hearing losses after experimental lesions in basal coil of cochlea. Arch Otolaryngol 1953; 57:129-42.

38. Schuknecht HF, Woellner RC. Hearing losses following partial section of the cochlear nerve. Laryngoscope 1953; 63: 441-65.

39. Sutton S, Schuknecht HF. Regional hearing losses from induced cochlear injuries in experimental animals. Ann Otol Rhinol Laryngol 1954; 63:727-53.

40. Hind JE, Schuknecht HF. A cortical test of auditory function in experimentally deaf cats. J Acoust Soc Am 1954; 26:89-97.

41. Schuknecht HF. Techniques for study of cochlear function and pathology in experimental animals. Development of the anatomical frequency scale for the cat. Arch Otolaryngol 1953; 58:377-97.

42. Schuknecht HF, Churchill JA, Doran R. The localization of acetylcholinesterase in the cochlea. Arch Otolaryngol 1959; 69:549-59.

43. Schuknecht HF. Pathology of the ear. Cambridge, Mass: Harvard University Press, 1974.

BASIC SCIENCE RESEARCHERS IN OTOLARYNGOLOGY AT THE UNIVERSITY OF CHICAGO

ROBERT A. BUTLER, PhD

I wish to begin by stating what I believe to have been the primary reasons why basic research has flourished in otolaryngology at the University of Chicago. First and foremost was Dr. Lindsay's own interest in and commitment to the endeavor. His long and illustrious career as an investigator has been reviewed by Drs. Schuknecht, Fredrickson, and Kohut (this supplement). The second reason, I believe, was his willingness to cooperate fully with colleagues in other departments, which led to a close collaboration with basic scientists. And finally, there was the University of Chicago itself, an institution with a rich tradition of research and scholarship.

How did John Lindsay go about placing research in otolaryngology on such a firm basis? Above all, he chose otolaryngologists with a strong research orientation to join the faculty. When he found such people, he followed Shakespeare's advice: "Grapple them to thy soul with hoops of steel." Dr. Fernández has already described the work of some of the pioneers. I wish, at this point, to add Dr. Naunton's name to the list of research-oriented clinicians brought here by Dr. Lindsay, although Ralph came many years after the pioneers. Ralph is a most competent investigator with a keen sense of critical analysis. His studies on electrocochleography in conjunction with Dr. Stanley Zerlin have received international recognition.[1] While chairman at Chicago, he carried on the Lindsay tradition by fostering and encouraging research activities of the staff and residents.

The professional interaction and close friendship that arose between Dr. Lindsay and Dr. Dewey Neff had widespread and almost profound ramifications. Harold Schuknecht, as a young assistant professor of otolaryngology, began experimental projects in Neff's laboratory. Classic papers on frequency analysis in the cochlea, studied by means of behavioral testing after selected lesions, resulted from this otolaryngology-biopsychology collaboration.[2,3] Dr. Lindsay, in turn, provided an electrophysiology laboratory in which two of Neff's graduate students could do the research for their PhD degrees. They were Joseph Hind[4] and Nelson Kiang;[5] each, in the introduction of his dissertation, acknowledged Dr. Lindsay's help and advice. To Dr. Lindsay's immense satisfaction, both carved out brilliant careers in the neurophysiology of hearing.

With clinician-investigators on board and multidisciplinary connections securely fixed, the foundation for launching a renowned research program was almost ready — but not quite. What was missing was a full-time researcher; one trained both in otolaryngology and in the biological sciences; one who had a flair for teaching; one whose research experience included active collaboration with such greats as Dr. Hallowell Davis and Dr. Ichiji Tasaki; one who could trace his scientific roots directly back to Ramon Cajal. Dr. Lindsay found him; the man, of course, was César Fernández.

When César arrived in 1954, research in Dr. Perlman's laboratory was already prospering on a full-time basis. Several papers on the circulation of the cochlea were being published.[6,7] An essential contributor to that enterprise was Robert Kimura, whose skill and impeccable standards in setting up what he considered to be an acceptable animal preparation left me in wonderment. Bob, as you know, has become an authority on electron microscopy of the inner ear. And I remind you that he was the first to devise an experimental procedure for producing labyrinthine hydrops in animals, thereby providing the long-sought-after animal model for systematic research on hydrops.[8]

Let us return to César Fernández. He has been an indefatigable worker. His enthusiasm is infectious; his technical skills are superb; and his knowledge of the anatomic, physiologic, and behavioral aspects of the auditory and vestibular systems has both depth and scope. He established an active laboratory designed for the study of cochlear potentials. The mission was to make explicit the interrelationship among the AC and DC potentials; to ferret out the meaningful electrical events leading to the initiation of the nerve impulse. His studies of the vestibular system have ranged from investigating the effects of selected lesions in the cerebellum on vestibular reflexes — good, solid work in which Dr. Lindsay was a close collaborator[9] — to his elegant studies of single-unit recordings from the peripheral and brainstem structures, for which he was awarded the coveted Bárány Gold Medal. Let me add immediately that César credits Jay Goldberg, another of Neff's former graduate students, with being indispensable to the success of the vestibular research program.[10-12]

I could go on at great length in describing the many different ways in which César Fernández implemented Dr. Lindsay's plan for a high-quality research center. It is not really a time constraint that inhibits me; rather, it is the thought of César's response the next time we are alone.

I was invited to join the research staff in 1957, and I jumped at the opportunity. Dr. Lindsay's continued support and the congenial colleagues in Otolaryngology contributed enormously toward making my career at the University of Chicago a marvelously rewarding experience. César said that I had to say something about my own work. I would like to think that my studies on auditory space perception may influence future theories on localization of sound in space.[13]

The next permanent addition to the research contingent was Dr. Raul Hinojosa. Raul's interest in temporal bone pathology was certainly consonant with that of Dr. Lindsay, and they worked closely together over the years.[14] Raul's most notable contributions have been his morphologic study of the stria vascularis[15] and his work on the comparative anatomy of the tangential nucleus.[16] Furthermore, he has carried the major responsibility for training our postdoctoral fellows during the past several years.

One of the consequences of Dr. Lindsay's worldwide reputation and his untiring efforts to see that our research findings gained a forum at national and international meetings was the influx of visiting scientists from abroad. The era when most of these visitors came to the University, from approximately 1958 to 1965, was for me the most exciting of times. Dr. Teruzo Konishi, an otolaryngologist from Japan, worked with us on cochlear electrophysiology. Konishi is truly a dedicated scientist, and what a great fortune it was to have him in the laboratory. In subsequent years, Dr. Konishi has distinguished himself through his work on receptor and neural potentials in the cochlea.[17-19] When he returned to Japan, I didn't think we would find another researcher with such remarkable surgical skills and perseverance. But we did, in the person of Dr. Vicente Honrubia, an otolaryngologist from Spain. Hence, the research on the electrical potentials in the cochlea continued without interruption, with Dr. Honrubia assuming responsibility for the microsurgical procedures. He, too, has become a well-known investigator of cochlear physiology[20] and, more recently, has been recognized for his work in applying computer technology to the testing of vestibular function in patients.[21]

During Dr. Honrubia's tenure at the University of Chicago, Dr. Brian Johnstone, an Australian biophysicist, arrived. In our laboratory, Johnstone learned about the intricacies of the cochlea, and he later became famous for his application of the Mössbauer technique to the study of frequency tuning in the cochlea, work that has important theoretical implications.[22]

From this brief, informal account of experimental work in otolaryngology at the University of Chicago, one underlying theme emerges; namely, that the accomplishments of the basic researchers working on the auditory and vestibular systems would not have been possible unless someone had set the stage upon which they acted. To his enduring credit, the man who brought this about was John Ralston Lindsay.

REFERENCES

1. Naunton RF, Zerlin S. Basis and some diagnostic implications of electrocochleography. Laryngoscope 1976; 86:475-82.

2. Schuknecht HF, Neff WD. Hearing losses after apical lesions in the cochlea. Acta Otolaryngol (Stockh) 1952; 42:263-74.

3. Schuknecht HF, Sutton S. Hearing losses after experimental lesions in basal coil of cochlea. Arch Otolaryngol 1953; 57:129-42.

4. Hind JE. An electrophysiological determination of tonotopic organization in auditory cortex of cat. J Neurophysiol 1953; 16:475-89.

5. Kiang NY. Discharge patterns of single fibers in the cat's auditory nerve. Cambridge, Mass: MIT Press, 1965.

6. Perlman HB, Kimura R. Experimental obstruction of the venous drainage and arterial supply of the inner ear. Ann Otol Rhinol Laryngol 1957; 66:537-46.

7. Kimura R, Perlman HB. Arterial obstruction of the labyrinth. Part I. Cochlear changes. Part II. Vestibular changes. Ann Otol Rhinol Laryngol 1958; 67:5-40.

8. Kimura R. Experimental blockage of the endolymphatic duct and sac and its effect on the inner ear of the guinea pig: a study on endolymphatic hydrops. Ann Otol Rhinol Laryngol 1967; 76:664-87.

9. Fernández C, Lindsay JR, Alzate R. Postural nystagmus due to localized cerebellar lesions in the cat. Acta Otolaryngol (Stockh) 1959; 50:287-90.

10. Goldberg JM, Fernández C. Physiology of peripheral neurons innervating semicircular canals of the squirrel monkey. I. Resting discharge and response to constant angular accelerations. J Neurophysiol 1971; 34:635-60.

11. Fernández C, Goldberg JM. Physiology of peripheral neurons innervating semicircular canals of the squirrel monkey. II. Response to sinusoidal stimulation and dynamics of peripheral vestibular system. J Neurophysiol 1971; 34:661-75.

12. Goldberg JM, Fernández C. Physiology of peripheral neurons innervating semicircular canals of the squirrel monkey. III. Variations among units in their discharge properties. J Neurophysiol 1971; 34:676-84.

13. Butler RA, Flannery R. The spatial attributes of stimulus frequency and their role in monaural localization of sound in the horizontal plane. Percept Psychophys 1980; 28:449-57.

14. Hinojosa R, Lindsay JR. Inner ear degeneration in Reye's syndrome. Arch Otolaryngol 1977; 103:634-40.

15. Hinojosa R, Rodriguez-Echandia EL. The fine structure of the stria vascularis of the cat inner ear. Am J Anat 1966; 118:631-64.

16. Hinojosa R, Robertson JD. Ultrastructure of the spoon type

synaptic endings in the nucleus vestibularis tangentialis of the chick. J Cell Biol 1967; 34:421-30.

17. Konishi T. Action of tubocurarine and atropine on the crossed olivocochlear bundles. Acta Otolaryngol (Stockh) 1972; 74:252-64.

18. Konishi T, Yasuno T. Summating potential of the cochlea in the guinea pig. J Acous Soc Am 1963; 35:1448-52.

19. Konishi T, Kelsey E. Effect of potassium deficiency on cochlear potentials and cation contents of the endolymph. Acta Otolaryngol (Stockh) 1973; 76:410-18.

20. Honrubia V, Ward PH. Longitudinal distribution of the cochlear microphonics inside the cochlear duct (guinea pig). J Acous Soc Am 1968; 44:951-8.

21. Honrubia V, Strelioff D, Ward PH. Computer analysis of induced vestibular and optokinetic nystagmus. Ann Otol Rhinol Laryngol 1971; 80:Suppl 3.

22. Johnstone BM, Boyle AJF. Basilar membrane vibration examined with the Mössbauer technique. Science 1967; 158:389-90.

CLINICAL RESEARCH IN OTOLARYNGOLOGY AT THE UNIVERSITY OF CHICAGO

RALPH F. NAUNTON, MD

John Lindsay and otolaryngology at the University of Chicago have always been and always will be synonymous; until December 1981, there had never been a time when John was not in the section, whether as chairman, as teacher, or as a member of the clinical or research staff.

It is difficult to distinguish definitionally and in all other ways between basic and clinical research, or between basic science and clinical investigators. The facile definition is that one type of research is done by the basic scientist, the other by the clinician. But this definition is "more honored in the breach than the observance." The facetious definition is that while clinical research is a white horse with black stripes, basic research is a black horse with white stripes. In other words, they are identical.

John Lindsay did not primarily train clinical investigators, nor did he primarily train basic science investigators. Nor, during the many years I knew him, was he primarily a clinician or primarily an investigator. He was each of these things and a master of each; but none can be identified as his primary contribution. What, then, was the contribution of this remarkable person, under whose direction the Section of Otolaryngology at the University of Chicago became a veritable Mecca to be visited, or to be revered from a distance? What was his primary skill or talent if it was not being a clinician or an investigator or a teacher of investigators?

I believe it was the wisdom to see, so many years ago, that the contemporary scientific training of the finest clinicians and the training of the finest biomedical investigators called, first and foremost, for an intellectual environment, an environment which he created by peopling the Section of Otolaryngology with such outstanding individuals as Robert Butler, César Fernández, Raul Hinojosa, William Ironside, Heinrich Kobrak, Santiago Riesco-McClure, Henry Perlman, and Joseph Wepman. This environment and the people contributing to it, together with the important catalytic action of its chief, John Lindsay, led to an inevitable phenomenon, the development of a school of young otolaryngologic clinicians and investigators of then unparalleled number and caliber.

In establishing this intellectual environment, John was supported to a valuable extent by the then developing National Institute of Neurological Diseases and Blindness (1950), later named the National Institute of Neurological Diseases and Stroke (1968), and still later, the National Institute of Neurological and Communicative Disorders and Stroke (1975). John's early, intimate involvement with the Institute played a major role in shaping its development as a mode of financial support for investigator trainees. He saw the first research fellowship and traineeship awarded in 1952, the first institute support for training programs in otolaryngology and pediatric neurology in 1957, and the first clinical research centers in communicative disorders supported in 1961. The support for Clinical Research Centers was intended to encourage the establishment of just such research environments as John envisaged, including delivery of the best of bedside and surgical care, the encouragement of clinical curiosity, laboratory research, and, most importantly, ongoing involvement with biomedical scientists of top caliber.

The value of this environment is well illustrated by the intellectual development and maturation of a biomedical investigator and clinician who died some years ago at a tragically early age. I refer to Carl Johner. Carl was recruited into the residency program in 1964 because of his outstanding promise as a physician and surgeon. But, from the outset, this honest individual vigorously declined to be involved in research — a dangerous position for any would-be entrant to the University of Chicago to take. Nevertheless he was accepted into the program, and the John Lindsay-created environment began to take effect. Carl first agreed to a brief period of research contact, then to a longer period of research involvement. Finally, he developed into a capable and productive investigator, studying, among other things, the influence of consciousness on the vestibular response to caloric stimulation[1] and the newly developing techniques of mediastinoscopy.[2-4] At the completion of his residency training, Carl was awarded an NIH Advanced Postdoctoral Research Fellowship and subsequently served as a junior staff member in the Section of Otolaryngology for a short period.

It is also eloquent testimony to the success of the John Lindsay-created training environment that teacher-investigators who were his pupils can be identified today in more than 20 academic departments of otolaryngology in this country and abroad.

John was thus working with phenomenal success in establishing a section of otolaryngology of outstanding strength at the University of Chicago; at the same time, he was working very deliberately to strengthen otolaryngology on a national scale.

We are all painfully aware of the flight of physicians from the ranks of biomedical investigators, both in this country and abroad. The reasons for this development, which may well be most severe in otolaryngology, are numerous and complex. Yet I dare to venture that, had the specialty of otolaryngology followed the example set by John Lindsay in the 1950s and 1960s at the University of Chicago, we would have a different story to tell today concerning biomedical research and the otolaryngologist's role in it. As I have indicated, John created an environment that was ideal for the training of biomedical investigators, for the training of physician-investigators, and for the scientifically based training of otolaryngologists whose ties with academia might well eventually weaken or even disappear. Too many programs failed to follow John Lindsay's example in its entirety, focusing only on the provision of scientifically based residency training while ignoring the training of physician-investigators. Thus, although there is probably an adequate supply of scientifically trained otolaryngologists, we find ourselves today suffering from a near-catastrophic dearth of capable physician-investigators in this specialty. Other medical and surgical specialties are beginning to experience similar problems.

I have spoken of John's contribution largely as if it had been mechanical, a matter of recognizing which scientists or clinicians he needed to populate and maintain this environment, and then merely a matter of devising the ways of ensuring their appointment and support. By delaying reference to John's personal contribution to this environment as clinician, investigator, and teacher, I have deliberately contrived to emphasize its importance. And I will use in describing that contribution the words of William G. Hale, one of the first head professors appointed by the University of Chicago's first President, William Rainey Harper. Hale wrote in 1896, shortly before John's birth:

> The leader of graduate students must not merely be a leader as toward them, while as toward the masters in his craft he is but a follower. He must himself be a master, or have the blood of mastery stirring in him. The professor that professes graduate work should be a man whose forum is, or at any rate is evidently soon to be, the world of scholars, the world over, in his province. This means that he must have the power of scientific divination. His scholarship must not be of the recipient type, but of the creative.[5]

Allow me to make one final comment as we search for suitable lasting ways to pay tribute to and memorialize John Lindsay's life and work. His greatest contribution lay in the creation of an environment for the training of physician-investigators. What better way to commemorate it than by the formal establishment, in the Pritzker School of Medicine, of a physician-investigator training program in John Lindsay's name? There is precedent for this approach to the problem of the disappearing physician-investigator in the establishment of programs of this type at the Duke University School of Medicine and the University of Pittsburgh School of Medicine. These programs are broad-based, avoiding the more usual narrow focus on a single investigative technique; they make generous, but not exclusive, use of the talents of PhDs who generally possess in-depth knowledge of the biomedical sciences and are therefore well-fitted to teach physician-investigator candidates; they also serve to bring PhDs into the mainstream by allowing them to develop major academic programs within schools of medicine. The curricula of these programs include basic laboratory techniques, cell, tissue, and organ culture, separation techniques, advanced instrumentation, enzymology, receptor and neurotransmitter chemistry, mathematics, teaching methods, and the preparation of manuscripts and grant applications.

Scientific methods will continue to change, but the need for biomedical research environments of the type John Lindsay envisaged and established will never diminish. A physician-investigator training program will ensure that this critical need is met in the Pritzker School of Medicine, and that the memory of this great man, who so vividly demonstrated the importance of the research environment, will be perpetuated by a living, dynamic, growing memorial.

REFERENCES

1. Johner CH, Perlman HB. Hypnosis and vestibular function. Ann Otol Rhinol Laryngol 1968; 77:126-38.

2. Johner CH, Conner GH, Procknow JJ. A comparison of mediastinoscopy and scalene node biopsy. Ann Otol Rhinol Laryngol 1967; 76:935-40.

3. Johner CH, Conner GH, Procknow JJ. Mediastinoscopy in experimental histoplasmosis. Arch Otolaryngol 1967; 86:326.

4. Johner CH. Mediastinal lymphography. Surg Gynecol Obstet 1968; 127:1313-6.

5. Hale WG. The graduate school. University of Chicago Record 1896; 1:439-41.

APPENDIX: PUBLICATIONS BY JOHN R. LINDSAY

JOURNAL ARTICLES

1. Lindsay JR, Walsh TE. Nasal secretions: the value of cytologic examination to the rhinologist. Arch Otolaryngol 1933; 17:783-86.

2. Lindsay JR. Cholesteatoma associated with an isolated perforation in Shrapnell's membrane. Arch Otolaryngol 1934; 20: 47-56.

3. Walsh TE, Lindsay JR. Cytology of nasal polypi. Arch Otolaryngol 1934; 20:649-58.

4. Kobrak HG, Lindsay JR, Perlman HB. Investigation of bone conduction in the animal and in the human. Laryngoscope 1935; 45:1-12.

5. Kobrak H, Lindsay JR, Perlman HB. Value of the reflex contraction of the muscles of the middle ear as an indicator of hearing. Arch Otolaryngol 1935; 21:663-76.

6. Kobrak H, Lindsay JR, Perlman HB. Acoustic stimulation of inner ear by application of sound into cavity of middle ear. Arch Otolaryngol 1936; 23:39-47.

7. Lindsay JR, Perlman HB. Paget's disease and deafness. Arch Otolaryngol 1936; 23:580-7.

8. Lindsay JR, Kobrak H, Perlman HB. Relation of the stapedius reflex to hearing sensation in man. Arch Otolaryngol 1936; 23:671-8.

9. Perlman HB, Lindsay JR. The utriculo-endolymphatic valve. Arch Otolaryngol 1936; 24:68-75.

10. Lindsay JR. Chronic sinusitis in children. Illinois Med J 1937; April:1-9.

11. Kobrak HG, Lindsay JR, Perlman HB, Dubner H. Effect of limited cochlear lesions on cochlear potentials and middle ear muscle reflexes. Arch Otolaryngol 1938; 27:59-66.

12. Lindsay JR. Suppuration in the petrous pyramid. Ann Otol Rhinol Laryngol 1938; 47:3-36.

13. Perlman HB, Lindsay JR. Relation of the internal ear spaces to the meninges. Arch Otolaryngol 1939; 29:12-23.

14. Lindsay JR. Petrous pyramid of temporal bone. Pneumatization and roentgenologic appearance. Arch Otolaryngol 1940; 31:231-55.

15. Kobrak HG, Lindsay JR, Perlman HB. The next step in auditory research. Arch Otolaryngol 1940; 31:467-77.

16. Lindsay JR. Laryngocele ventricularis. Ann Otol Rhinol Laryngol 1940; 49:661-74.

17. Lindsay JR. Chemotherapy in the treatment of complications of acute middle ear suppuration (petrositis and meningitis). Ann Otol Rhinol Laryngol 1941; 50:159-77.

18. Lindsay JR. The early diagnosis of carcinoma of the esophagus. Ann Otol Rhinol Laryngol 1941; 50:675-80.

19. Lindsay JR. Pneumatization of the petrous pyramid. Ann Otol Rhinol Laryngol 1941; 50:1109-13.

20. Eichelberger L, Lindsay JR. Chemical composition of fluids from benign cysts of the antrum. Proc Soc Exp Biol Med 1941; 47:191-5.

21. Kobrak HG, Lindsay JR, Perlman HB. Experimental observations on the question of auditory fatigue. Laryngoscope 1941; 51:1-12.

22. Lindsay JR. Nonsecreting cysts of the maxillary sinus mucosa. Laryngoscope 1942; 52:84-100.

23. Proctor B, Lindsay JR. Tuberculosis of the ear. Arch Otolaryngol 1942; 35:221-49.

24. Lindsay JR. Labyrinthine dropsy and Ménière's disease. Arch Otolaryngol 1942; 35:853-67.

25. Lindsay JR. Thrombosis of intracranial venous sinuses in middle ear suppuration. Illinois Med J 1942; 81:467-84.

26. Lindsay JR. Meniere's disease, or labyrinthine hydrops. Minn Med 1942; 25:498-500.

27. Proctor B, Lindsay JR, Gonne WS. Sequestration of the osseous labyrinth. Arch Otolaryngol 1943; 37:819-30.

28. Lindsay JR. Eustachian tube function and deafness. Minn Med 1943; 26:250-7.

29. Lindsay JR. Meniere's symptom complex, differential diagnosis and treatment. Trans Indiana Acad Ophthalmol Otolaryngol 1943; April:1-12.

30. Lindsay JR, Judd DK. Observations on the local use of sulfonamides and tyrothricin in the upper respiratory tract. Trans Am Acad Ophthalmol Otolaryngol 1943; 47:431-9.

31. Lindsay JR, Templeton FE, Rothman S. Lesions of the esophagus in generalized progressive scleroderma. JAMA 1943; 123:745-50.

32. Lindsay JR, Morgan RH, Wepman JM. The cricopharyngeus muscle in esophageal speech. Laryngoscope 1944; 54:55-65.

33. Lindsay JR. Ménière's disease. Histopathologic observations. Arch Otolaryngol 1944; 39:313-8.

34. Lindsay JR. Recent progress in management of acute suppuration of the middle ear. Arch Otolaryngol 1944; 39:492-7.

35. Lindsay JR, Oppenheimer MJ, Wycis HT, Spiegel EA. Receptor apparatus of the vestibulovasomotor reaction. Arch Otolaryngol 1945; 42:257-66.

36. Lindsay JR. Osteomyelitis of the petrous pyramid of the temporal bone. Ann Surg 1945; 122:1060-70.

37. Lindsay JR. The significance of a positional nystagmus in otoneurological diagnosis. Laryngoscope 1945; 55:527-53.

38. Lindsay JR. Meniere's syndrome. J Indiana Med Assoc 1946; 39:23-40.

39. Lindsay JR. Histologic observations on the healing of labyrinthine fistulas in monkeys. Arch Otolaryngol 1946; 43: 37-48

40. Lindsay JR. Labyrinthine dropsy. Laryngoscope 1946; 56: 325-41.

41. Brunschwig A, Lindsay JR. Further experiences with panlaryngectomy for advanced carcinoma of the larynx. Surg Gynecol Obstet 1946; 83:639-42.

42. Lindsay JR. Effect of obliteration of the endolymphatic sac and duct in the monkey. Arch Otolaryngol 1947; 45:1-13.

43. Lindsay JR. The fenestration operation. Observations on the evaluation of hearing tests. Laryngoscope 1947; 57:367-80.

44. Proctor B, Lindsay JR. Tumors involving the petrous pyramid of the temporal bone. Arch Otolaryngol 1947; 46: 180-94.

45. Lindsay JR. Healing of experimental labyrinthine fistulas: further observations. Arch Otolaryngol 1947; 46: 584-600.

46. Lindsay JR. Pathology of vertigo arising from the peripheral vestibular apparatus. Ann Otol Rhinol Laryngol 1947; 56: 541-54.

47. Lindsay JR. Meniere's syndrome: differential diagnosis and treatment. Mississippi Doctor 1947; May:6-10.

48. Lindsay JR. The significance of postural vertigo in otoneurological diagnosis. Mississippi Doctor 1948; January:365-8.

49. Lindsay JR, Schuknecht HF. Intracranial complications in otolaryngology. Arch Otolaryngol 1948; 48:597-608.

50. Lindsay JR. Labyrinthine surgery for Meniere's disease. Laryngoscope 1949; 59:22-34.

51. Lindsay JR. Esophageal lesions in diffuse scleroderma. Laryngoscope 1949; 59:83-112.

52. Day KM, Lindsay JR. Hydrops of the labyrinth. Case report. Coagulation operation, clinical course and histopathology. Laryngoscope 1949; 59:213-27.

53. Schuknecht HF, Lindsay JR. Benign cysts of the paranasal sinuses. Arch Otolaryngol 1949; 49:609-30.

54. Lindsay JR, Zuidema JJ. Inner ear deafness of sudden onset. Laryngoscope 1950; 60:238-63.

55. Lindsay JR, Perlman HB. Tests for chronic eustachian tube obstruction. Trans Am Acad Ophthalmol Otolaryngol 1950; 54: 486-491.

56. Lindsay JR. Vertigo. Differential diagnosis and treatment. Wis Med J 1950; July.

57. Lindsay JR. The influence of systemic and local factors on the development of otosclerosis. Trans Am Acad Ophthalmol Otolaryngol 1950; Nov. Suppl:23-28.

58. Lindsay JR. Influence of systemic and local factors on the development of otosclerosis. Arch Otolaryngol 1950; 52:368-81.

59. Lindsay JR, Perlman HB. Sarcoidosis of the upper respiratory tract. Ann Otol Rhinol Laryngol 1951; 60:549-66.

60. Lindsay JR. Postural vertigo and positional nystagmus. Ann Otol Rhinol Laryngol 1951; 60:1134-52.

61. Lindsay JR. The differential diagnosis of vertigo. Vet Admin Tech Bull 1951; TB 10-78.

62. Lindsay JR, Schuknecht HF, Neff WD, Kimura RS. Obliteration of the endolymphatic sac and the cochlear aqueduct. Ann Otol Rhinol Laryngol 1952; 61:697-716.

63. Lindsay JR. Some experimental observations bearing on Meniere's disease. Trans Am Acad Ophthalmol Otolaryngol 1953; 57:27-34.

64. Lindsay JR. The pathogenesis of cholesteatoma and summary of discussions on the removal of the matrix. Trans Am Acad Ophthalmol Otolaryngol 1953; 57:707-10.

65. Lindsay JR, Caruthers DG, Hemenway WG, Harrison S. Inner ear pathology following maternal rubella. Ann Otol Rhinol Laryngol 1953; 62:1201-18.

66. Lindsay JR, Neff WD, Schuknecht HF, Perlman HB. Obliteration of the ductus endolymphaticus and their accompanying venous channels. Acta Otolaryngol (Stockh) 1953; 43: 176-89.

67. Lindsay JR, Hemenway WG. Occlusion of the round window by otosclerosis. Trans Am Acad Ophthalmol Otolaryngol 1954; 58:439-47.

68. Lindsay JR, Hemenway WG. Occlusion of the round window by otosclerosis. Laryngoscope 1954; 64:10-19.

69. Lindsay JR, Harrison RS. The pathology of rubella deafness. J Laryngol Otol 1954; 68:461-4.

70. Lindsay JR, Hemenway WG. Inner ear pathology due to measles. Ann Otol Rhinol Laryngol 1954; 63:754-71.

71. Lindsay JR. The dizzy patient. Kansas City Med J 1955; 31:18-23.

72. Lindsay JR. The practical management of dizziness. California Med 1955; 83:193.

73. Lindsay JR, Siedentop KH. Labyrinthine surgery in the treatment of Meniere's disease. Ann Otol Rhinol Laryngol 1955; 64:69-78.

74. Lindsay JR. Functional disturbances of the upper swallowing mechanism. Ann Otol Rhinol Laryngol 1955; 64: 766-76.

75. Lindsay JR, Ironside WMS. Carcinoma of the larynx, classification and results of treatment. Laryngoscope 1955; 65: 1117-28.

76. Lindsay JR. Pathology. Symposium: Meniere's disease. Trans Am Acad Ophthalmol Otolaryngol 1956; 60:172-6.

77. Lindsay JR. Is voluntary teaching on the way out? Trans Am Acad Ophthalmol Otolaryngol 1956; 60:231-4.

78. Lindsay JR. Temporal bones for microscopic study. Trans Am Acad Ophthalmol Otolaryngol 1956; 60:732-4.

79. Lindsay JR, Hemenway WG. Postural vertigo due to unilateral sudden partial loss of vestibular function. Ann Otol Rhinol Laryngol 1956; 65:692-706.

80. Meltzer PE, Lindsay JR, Goodhill V, Shambaugh GE, Kos CM, Fowler EP Jr. Symposium: The operation for the mobilization of the stapes in otosclerotic deafness. Laryngoscope 1956; 66:729-84.

81. Lindsay JR, von Schulthess G. An unusual case of labyrinthine hydrops. Acta Otolaryngol (Stockh) 1958; 49: 315-24.

82. Fernández C, Allen GW, Lindsay JR. Experimental studies in fixation of the stapes and fenestra ovalis. Laryngoscope 1958; 68:1881-1907.

83. Lindsay JR. Transmission and transduction in the cochlea. Clinical discussion. Laryngoscope 1958; 68:385-8.

84. Lindsay JR. Sudden deafness due to virus infection. Arch Otolaryngol 1959; 69:13-8.

85. Fernández C, Lindsay JR, Alzate R. Postural nystagmus due to localized cerebellar lesions in the cat. Acta Otolaryngol (Stockh) 1959; 50:287-90.

86. Lindsay JR, Hilding AC, McLaurin JW, Keeler NS, House HM. Histopathologic changes following fenestration and stapes mobilization. Trans Am Acad Ophthalmol Otolaryngol 1959; 63:187-205.

87. Fernández C, Lindsay JR, Moskowitz M. Some observations on the pathogenesis of middle-ear cholesteatoma. Arch Otolaryngol 1959; 69:537-46.

88. Ironside WMS, Lindsay JR. Ultrasonic therapy for relief of vertigo due to Meniere's disease. Laryngoscope 1959; 69: 899-913.

89. Ironside WMS, Carpender JWJ, Roedal R, Lindsay JR. Carcinoma of the larynx. Results obtained by surgery and external radiation in ninety-three cases. JAMA 1959; 169:783-6.

90. Fernández C, Alzate R, Lindsay JR. Experimental observations on postural nystagmus in the cat. Ann Otol Rhinol Laryngol 1959; 68:816-29.

91. Hemenway WG, Lindsay JR. Malignancies of the paranasal sinuses. Arch Otolaryngol 1959; 70:61-4.

92. Fernández C, Alzate R, Lindsay JR. Experimental observations on postural nystagmus. II. Lesions of the nodulus. Ann Otol Rhinol Laryngol 1960; 69:94-114.

93. Lindsay JR. Experimental stapes fixation and fenestra ovalis. Arch Otolaryngol 1960; 71:217-23.

94. Lindsay JR, Davey PR, Ward PH. Inner ear pathology in deafness due to mumps. Ann Otol Rhinol Laryngol 1960; 69: 918-35.

95. Lindsay JR. Hydrops of the labyrinth. Arch Otolaryngol 1960; 71:500-10.

96. Lindsay JR, Proctor LR, Work WP. Histopathologic inner ear changes in deafness due to neomycin in a human. Laryngoscope 1960; 70:382-92.

97. Fernández C, Lindsay JR. Positional nystagmus in man and animals. J Nerv Ment Dis 1960; 130:488-95.

98. Fernández C, Lindsay JR. Aural cholesteatoma. Experimental observations. Laryngoscope 1960; 70:1119-41.

99. Lindsay JR. Deafness and dizziness. Med Times 1960; 88:699-701.

100. Lindsay JR, Sanders SH, Nager GT. Histopathologic observations in so-called congenital fixation of the stapedial footplate. Laryngoscope 1960; 70:1587-1602.

101. Lindsay JR. Histopathologic findings following stapedectomy and polyethylene tube inserts in the human. Ann Otol Rhinol Laryngol 1961; 70:785-807.

102. Lindsay JR. Should residents do research? Symposium: Residency training. Trans Am Acad Ophthalmol Otolaryngol 1962; 66:123-6.

103. Lindsay JR. The temporal bone banks for ear research program. Trans Am Acad Ophthalmol Otolaryngol 1962; 66: 211-3.

104. Fernández C, Lindsay JR. The vestibular system. Progress report. Arch Otolaryngol 1962; 75:276-8.

105. Ward PH, Kinney CE, Lindsay JR. Inner ear pathology in congenital deafness. Laryngoscope 1962; 72:435-55.

106. Fernández C, Lindsay JR. The vestibular efferent system. Progress report. Arch Otolaryngol 1963; 77:449-51.

107. Lindsay JR. Is federal support of research desirable? Trans Am Acad Ophthalmol Otolaryngol 1963; 67:24-7.

108. Lindsay JR. Summary: Stapes surgery. Arch Otolaryngol 1963; 78:625-6.

109. Lindsay JR. Mastoiditis. Postgrad Med 1963; 34:A75-80.

110. Fredrickson JM, Griffith AW, Lindsay JR. Transverse fracture of the temporal bone. A clinical and histopathological study. Arch Otolaryngol 1963; 78:770-84.

111. Lindsay JR. Relation of otology to neurology. Symposium: Neurology and the sense organs. Trans Am Acad Ophthalmol Otolaryngol 1964; 68:198-203.

112. Baron SH, Lindsay JR. Stapedectomy with fat graft and polyethylene strut. Arch Otolaryngol 1964; 80:128-30.

113. Fernández C, Lindsay JR. The vestibular coriolis reaction. Arch Otolaryngol 1964; 80:469-72.

114. Beal DD, Lindsay JR, Ward PH. Radiation-induced carcinoma of the mastoid. Arch Otolaryngol 1965; 81:9-16.

115. Lindsay JR. Training in otolaryngology. Address of the President. Trans Am Acad Ophthalmol Otolaryngol 1965; 69: 9-11.

116. Ward PH, Lindsay JR, Warner NE. Cytomegalic inclusion disease affecting the temporal bone. Laryngoscope 1965; 75:628-38.

117. Kohut RI, Lindsay JR. Glomus jugulare tumors. New techniques for determining operability. Laryngoscope 1965; 75: 750-62.

118. Ward PH, Cannon D, Lindsay JR. The vestibular system in multiple sclerosis. A clinical-histopathological study. Laryngoscope 1965; 75:1031-47.

119. Fernández C, Lindsay JR. Vestibular tests: methods of recording eye movements. Progress report. Arch Otolaryngol 1965; 82:664-6.

120. Lindsay JR, Conner GH. Microsurgery of the ear. Surg Clin North Am 1966; 46:111-30.

121. Lindsay JR, Beal DD. Sensorineural deafness in otosclerosis. Observations on histopathology. Ann Otol Rhinol Laryngol 1966; 75:436-57.

122. Lindsay JR, Matz GJ. The differentiation of acquired congenital from genetically determined inner ear deafness. Ann Otol Rhinol Laryngol 1966; 75:830-43.

123. Beal DD, Davey PR, Lindsay JR. Inner ear pathology of congenital deafness. Arch Otolaryngol 1967; 85:134-42.

124. Lindsay JR, Kohut RI, Sciarra PA. Menière's disease: pathology and manifestations. Ann Otol Rhinol Laryngol 1967; 76: 5-22.

125. Lindsay JR. Viral labyrinthitis — histopathologic characteristics. Acta Otolaryngol (Stockh) 1967; 63:138-43.

126. Lindsay JR. Paroxysmal postural vertigo and vestibular neuronitis. Arch Otolaryngol 1967; 85:544-7.

127. Lindsay JR. Postural vertigo. Minn Med 1967; 50:1013-5.

128. Lindsay JR. Histopathologic characteristics of viral labyrinthitis. Otologia Fukuoka 1967; 13:77-91.

129. Beal DD, Hemenway WG, Lindsay JR. Inner ear pathology of sudden deafness. Arch Otolaryngol 1967; 85:591-8.

130. Matz GJ, Lockhart HB, Lindsay JR. Meningitis following stapedectomy. Laryngoscope 1968; 78:56-63.

131. Henneford GE, Lindsay JR. Deaf-mutism due to meningogenic labyrinthitis. Laryngoscope 1968; 78:251-61.

132. Lindsay JR. Pathology of vestibular disorders. Vertigo of peripheral origin: histopathology. Ann Otol Rhinol Laryngol 1968; 77:203-9.

133. Lindsay JR. Histopathology of Meniere's disease as observed by light microscopy. Otolaryngol Clin North Am 1968; 1:319-29.

134. Lindsay JR. Some highlights of the early history of Chicago. Acta Otolaryngol (Stockh) 1968; 65:3-8.

135. Lindsay JR, Lehman RH. Histopathology of the temporal bone in advanced Paget's disease. Laryngoscope 1969; 79:213-27.

136. Lindsay JR. Progress in otorhinolaryngology. Illinois Med J 1969; May:565-71.

137. Valvassori GE, Naunton RF, Lindsay JR. Inner ear anomalies: clinical and histopathological considerations. Ann Otol Rhinol Laryngol 1969; 78:929-38.

138. Cohn AM, Sataloff J, Lindsay JR. Histiocytosis X (Letterer-Siwe disease) with involvement of the inner ear. Arch Otolaryngol 1970; 91:24-9.

139. Lindsay JR, Zajtchuk J. Concussion of the inner ear. Ann Otol Rhinol Laryngol 1970; 79:699-709.

140. Cohn AM, House HP, Lindsay JR. Deafness in early childhood. Laryngoscope 1970; 80:1665-79.

141. Lindsay JR. Inner ear pathology in congenital deafness. Otolaryngol Clin North Am 1971; 4:249-90.

142. Kohut RI, Lindsay JR. Pathologic changes in idiopathic labyrinthine hydrops. Acta Otolaryngol (Stockh) 1972; 73: 402-12.

143. Zajtchuk JT, Matz GJ, Lindsay JR. Temporal bone pathology in herpes oticus. Ann Otol Rhinol Laryngol 1972; 81: 331-8.

144. Lindsay JR. Histopathology of otosclerosis. Arch Otolaryngol 1973; 97:24-9.

145. Naunton RF, Lindsay JR, Stein LK. Concretions in the stria vascularis. Arch Otolaryngol 1973; 97:376-80.

146. Lindsay JR. Histopathology of deafness due to post-natal viral disease. Arch Otolaryngol 1973; 98:258-64.

147. Lindsay JR. Profound childhood deafness. Inner ear pathology. Ann Otol Rhinol Laryngol 1973; 82 Suppl 5:1-121.

148. Lindsay JR. Blue mantles in otosclerosis. Ann Otol Rhinol Laryngol 1974; 83:33-42.

149. Lindsay JR. Histopathology of otosclerosis. Arch Otolaryngol 1973; 97:24-9.

150. Lindsay JR, Black FO, Donnelly WH Jr. Acrocephalosyndactyly (Apert's syndrome): temporal bone findings. Ann Otol Rhinol Laryngol 1975; 84:174-8.

151. Suga F, Lindsay JR. Labyrinthitis ossificans due to chronic otitis media. Ann Otol Rhinol Laryngol 1975; 84:37-44.

152. Zajtchuk JT, Lindsay JR. Osteogenesis imperfecta congenita and tarda: a temporal bone report. Ann Otol Rhinol Laryngol 1975; 84:350-8.

153. Hipskind MM, Lindsay JR, Valvassori GE. Recurrent meningitis and labyrinthine gusher, related to congenital defects of the labyrinthine capsule and stapes footplate. Laryngoscope 1976; 86:682-9.

154. Lindsay JR, Suga F. Sensorineural deafness due to osteitis fibrosa. Arch Otolaryngol 1976; 102:37-42.

155. Suga F, Lindsay JR. Histopathological observations of presbycusis. Ann Otol Rhinol Laryngol 1976; 85:169-84.

156. Suga F, Lindsay JR. Inner ear degeneration in acoustic neurinoma. Ann Otol Rhinol Laryngol 1976; 85:343-58.

157. Fitch N, Lindsay JR, Srolovitz H. The temporal bone in the preauricular pit, cervical fistula, hearing loss syndrome. Ann Otol Rhinol Laryngol 1976; 85:268-75.

158. Suga F, Lindsay JR. Temporal bone histopathology of osteopetrosis. Ann Otol Rhinol Laryngol 1976; 85:15-24.

159. Lindsay JR, Suga F. Paget's disease and sensorineural deafness: temporal bone histopathology of Paget's disease. Laryngoscope 1976; 86:1029-42.

160. Lindsay JR, Hinojosa R. Histopathologic features of the inner ear associated with Kearns-Sayre syndrome. Arch Otolaryngol 1976; 102:747-52.

161. Suga F, Lindsay JR. Labyrinthitis ossificans. Ann Otol Rhinol Laryngol 1977; 86:17-29.

162. Hinojosa R, Lindsay JR. Inner ear degeneration in Reye's syndrome. Arch Otolaryngol 1977; 103:634-40.

163. Lindsay JR, Hinojosa R. Ear anomalies associated with renal dysplasia and immunodeficiency disease. Ann Otol Rhinol Laryngol 1978; 87:10-7.

164. Kohut RI, Lindsay JR. Necrotizing ("malignant") external otitis. Histopathologic processes. Ann Otol Rhinol Laryngol 1979; 88:714-20.

165. Hinojosa R, Lindsay JR. Profound deafness. Associated sensory and neural degeneration. Arch Otolaryngol 1980; 106: 193-209.

BOOKS AND BOOK CHAPTERS

1. Lindsay JR, Perlman HB. Otoneurology. In: Spiegel EZ, ed. Progress in neurology and psychiatry. Vol II, 1947, 119-30; Vol III, 1948, 151-62; Vol IV, 1949, 155-62; Vol V, 1950. 168-76; Vol VI, 1951, 139-47; Vol XI, 1956, 51-7; Vol XIII, 1958, 64-71; Vol XIV, 1959, 186-92; Vol XV, 1960, 170-5; Vol XXV, 1970, 159-66. New York: Grune and Stratton.

2. Perlman HB, Lindsay JR. Otoneurology. In: Spiegel EZ, ed. Progress in neurology and psychiatry. Vol VII, 1952, 169-79; Vol XII, 1957, 171-9; Vol XVI, 1961, 163-9; Vol XVII, 1962, 164-71; Vol XVIII, 1963, 224-8; Vol XIX, 1964, 254-60; Vol XX, 1965, 261-9; Vol XXI, 1966, 188-94; Vol XXII, 1967, 190-5; Vol XXIII, 1968, 198-202; Vol XXIV, 1969, 182-8. New York: Grune and Stratton.

3. Lindsay JR. Suppurative labyrinthitis. In: Jackson C, Jackson CL, eds. Diseases of the nose, throat, and ear. Philadelphia: WB Saunders, 1945:395; 1959:521-9.

4. Lindsay JR. The diagnosis of hydrops of the labyrinth. In: Wiener M, Maumenee AE, Ireland PE, Sullivan JA, eds. Progress in ophthalmology and otolaryngology. Vol I, chap 6. New York: Grune and Stratton, 1952, 417-28.

5. Vail D, Lindsay JR, eds. The year book of the eye, ear, nose and throat. Chicago: Year Book Medical Publishers, 1951-1957.

6. Lindsay JR, Perlman HB, Kobrak HG, Neff WD. Physiology of the ear. In: Coates GM, Schenck HP, Miller MV, eds. Otolaryngology. Vol I, chap 3. Hagerstown, Maryland: W. F. Prior, 1957.

7. Lindsay JR. Postural vertigo: a Meniere-like syndrome. In: The medical clinics of North America. Philadelphia: WB Saunders, 1958:547-54.

8. Lindsay JR, Lierle D, Huffman WC, eds. The year book of the ear, nose and throat. Chicago: Year Book Medical Publishers, 1957-1968.

9. Lindsay JR, Lierle DM, eds. The year book of the ear, nose and throat. Chicago: Year Book Medical Publishers, 1969.

10. Fernández C, Alzate R, Lindsay JR. Interrelations between flocculonodular lobe and vestibular system. In: Rasmussen GL, Windle WF, eds. Neural mechanisms of the auditory and vestibular systems. Springfield, Ill: Charles C Thomas, 1960, chap 21: 285-96.

11. Lindsay JR. Report of the panel on vertigo. In: Forster FM, ed. Evaluation of drug therapy. Madison: University of Wisconsin Press, 1961:99-106.

12. Lindsay JR. Histopathology in autopsy specimens after stapes surgery. In: Henry Ford Hospital international symposium on otosclerosis. Chap 30. Boston: Little, Brown & Co, 1962: 359-70.

13. Lindsay JR. Summarization of the symposium. In: Henry Ford Hospital international symposium on otosclerosis. Chap 50. Boston: Little, Brown & Co, 1962:643-6.

14. Lindsay JR. Pathology of Meniere's disease. In: Spector M, ed. Dizziness and vertigo. Chap 6. New York: Grune and Stratton, 1966; 123-33.

15. Lindsay JR. Labyrinthitis of viral origin. In: Sensorineural hearing processes and disorders. Boston: Little, Brown & Co, 1967; 445-50.

16. Lindsay JR. Viral labyrinthitis—histopathologic characteristics. Symp ORL Iug 1967; 1-2:465-9.

17. Lindsay JR. Hydrops of the labyrinth. Idiopathic and secondary types. Symp ORL Iug 1967; 1-2:488-90.

18. Lindsay JR. Inner ear histopathology in genetically determined congenital deafness. In: The clinical delineation of birth defects. Part IX (Ear). Vol 7. Baltimore: Williams and Wilkins, 1971:21-32.

19. Lindsay JR. Inner ear pathology in congenital deafness. In: Otolaryngologic clinics of North America. Vol 4. Philadelphia: WB Saunders, 1971:249-90.

20. Lindsay JR. Otosclerosis. Histopathology. In: Paparella MM and Shumrick DA, eds. Textbook of ear, nose, and throat. Vol 2, chap 14. Philadelphia: WB Saunders, 1973:205-30.

21. Lindsay JR. Nerve deafness related to cholesteatoma. In: McCabe BF, Sadé J, Abramson M, eds. Cholesteatoma, first international conference. Chap 9. Birmingham, Ala: Aesculapius, 1977:452-62.

22. Lindsay JR. Pathology of the peripheral vestibular system in the human. In: Naunton RF, ed. The vestibular system. New York: Academic Press, 1975, 379-95.

23. Lindsay JR, Hinojosa R. The acoustic ganglion in profound sensorineural deafness. In: Naunton RF, Fernández C, eds. Evoked electrical activity in the auditory nervous system. New York: Academic Press, 1978, 301-21.

24. Lindsay JR. Otosclerosis. In: Paparella MM, Shumrick DA, eds. Otolaryngology, 2nd ed. Vol II, chap 25. Philadelphia: WB Saunders, 1980:1617-44.

25. Hinojosa R, Lindsay JR, Matz GJ, Naunton RF. The inner ear. In: Ridell RH, ed. Pathology of drug-induced and toxic diseases. Chap 8. New York: Churchill Livingstone, 1982:155-66.

ANNALS PUBLISHING COMPANY
4507 LACLEDE AVENUE
ST LOUIS, MISSOURI 63108
COPYRIGHT 1983, ANNALS PUBLISHING COMPANY

Acc.
23.6.83

COCHLEAR PATHOLOGY IN CHRONIC SUPPURATIVE OTITIS MEDIA

A. PETER WALBY, FRCS (ED)

ALFONSO BARRERA, MD

HAROLD F. SCHUKNECHT, MD

LIBRARY

Supplement 103 — Vol. 92, March-April 1983, No. 2, Part 2

ANNALS OF OTOLOGY, RHINOLOGY & LARYNGOLOGY

ANNALS OF HEAD & NECK MEDICINE & SURGERY

COCHLEAR PATHOLOGY
IN
CHRONIC SUPPURATIVE OTITIS MEDIA

A. Peter Walby, FRCS (Ed)

Alfonso Barrera, MD

Harold F. Schuknecht, MD

COCHLEAR PATHOLOGY IN CHRONIC SUPPURATIVE OTITIS MEDIA

A. PETER WALBY, FRCS (ED)
BELFAST, NORTHERN IRELAND

ALFONSO BARRERA, MD
BOSTON, MASSACHUSETTS

HAROLD F. SCHUKNECHT, MD
BOSTON, MASSACHUSETTS

Chronic suppurative otitis media (COM) is reported to cause elevation of bone-conduction thresholds either by damage to cochlear sensorineural structures or by alteration in the mechanics of sound transmission in the ear. A retrospective study was made of the medical records of 87 patients with unilateral uncomplicated COM to document that abnormality in bone conduction does exist. In a separate study the cochlear pathology in 12 pairs of temporal bones with unilateral COM was studied by light microscopy. Infected ears showed higher than normal mean bone-conduction thresholds by amounts ranging from 1 dB at 500 Hz to 9.5 dB at 4,000 Hz. The temporal bones showed no greater loss of specialized sensorineural structures in infected ears than in normal control ears. Because there is no evidence that COM caused destruction of hair cells or cochlear neurons, alteration in the mechanics of sound transmission becomes a more plausible explanation for the hearing losses.

INTRODUCTION

Chronic suppurative otitis media (COM) is thought of by most clinicians as a destructive process which commonly causes conductive hearing losses but may occasionally result in a sensorineural hearing loss. It is not commonly recognized that the mechanism of the effect on inner ear function has not been clearly established in all cases. Tympanogenic suppurative labyrinthitis frequently causes a severe sensorineural hearing loss with destruction of sensory and neural elements in the cochlea, which may progress to osseous obliteration of the labyrinth.[1] A mild serous labyrinthitis may cause a transient elevation in bone conduction thresholds without these obvious permanent effects on the cochlea, but the pathology is not well understood.[1] This study was designed to investigate whether chronic bacterial infection of the middle ear that shows apparent signs of sensorineural deafness actually results in loss of sensorineural elements in the inner ear.

Studies on patients with COM have used bone conduction as a measure of inner ear function. Hůlka[2] in 1941 measured changes in bone conduction thresholds which occurred in 23 patients following an acute exacerbation of COM. There was a tendency for altered bone conduction thresholds (increased at high frequencies and decreased at low frequencies) to return when healed to levels measured just at the onset of the exacerbation. It was suggested that the transient changes may have been caused by toxins penetrating through the promontory to the basal turn of the cochlea, but it was also recognized that alteration of middle or inner ear mechanics might have affected the measured bone conduction. Lierle and Reger[3] recognized a similar change in shape of the audiogram, but they found it a relatively rare occurrence. Later Carhart[4] confirmed the audiological findings but cautioned that distortions of the bone conduction curve could occur for mechanical reasons even in the absence of sensorineural loss.

Gardenghi[5] in 1955 found 22 of 50 patients with COM to have "a perceptive hypoacusis confirmed by the presence of recruitment." Bluvshtein[6] in 1963 reported on 300 patients with COM and found normal bone conduction in 65.2%, 10 to 15 dB loss in 12.4%, and greater than 30 dB loss in 16%. Schuknecht[7] recognized that a descending audiometric curve was frequently found in patients with COM, but attempts by light microscopy to find an inner ear structural correlate failed.

Paparella et al[8] reported a retrospective study of 279 cases of COM in which abnormally high bone conduction thresholds were observed. Cases where there was another apparent factor which could cause a sensorineural hearing loss were said to be excluded. In 32 patients aged 20 to 50 years with unilateral COM there was a difference in bone conduction threshold between the normal and infected ears of about 3 dB at 500 Hz, 7 dB at 1,000 Hz, 11 dB at 2,000 Hz, and 15 dB at 4,000 Hz, uniformly worse in the infected ear. Statistical tests of significance had indicated that this difference was unlikely to have arisen by chance at the upper three frequencies ($p<0.01$), but at 500 Hz it was not significant. Cases with a normal control ear were used to help exclude presbycusis. It was suggested that because increased bone conduction thresholds may persist after surgery, with removal of overlying patholog-

---

From the Harvard Medical School and Massachusetts Eye and Ear Infirmary, Boston. Dr. Walby is now with the Department of Otolaryngology, Royal Victoria Hospital, Belfast.

This work was supported by NINCDS Grant 5 R01 NS05881-16 and the Northern Ireland Council for Postgraduate Medical Education.

ical middle ear tissue, window occlusion was not the cause of the raised levels. Paparella considered the increased bone conduction thresholds to reflect "insidious sensorineural losses" which he thought to be best explained by biochemical alteration of the perilymph and endolymph due to substances traversing the round window membrane. It was concluded that it was important to assess cochlear function serially in cases of COM and "initiate prompt and proper therapy to avert permanent cochlear damage."

In 1972, Paparella et al[9] reported a histopathological study of otitis media. Of 344 human temporal bones examined, 13 (mostly adults) were classified as having COM. Serofibrinous precipitates were seen in the perilymph of the scala tympani in four cases, inflammatory cells in four, and both in two cases. Quantitative hair cell analysis by cochlear graphic reconstruction was possible in only one case, because ten had "hypotonic degeneration" and two had "autolysis." One case, a child, had good hair cell preservation and showed scattered losses in the lower basal turn. Five of those with hypotonic degeneration "seemed to have lower basal turn lesions," but it was noted that presbycusis had not been ruled out as the cause. Examination of other cochlear structures was not reported and no mention was made of comparisons with the opposite ears. Paparella concluded that when sensorineural hearing loss develops in COM, "active surgical or medical treatment should be considered if not already done."

In 1973 English et al[10] reported on 404 patients with COM and found increased duration of infection and bone conduction losses of increasing severity in those with more marked middle ear pathology as assessed clinically. Only patients younger than 42 were included in the study, and any case with a known history that might implicate certain other possible causes of sensorineural deafness was excluded. Only the diseased ears were evaluated.

Meyerhoff et al[11] reviewed 800 pathological temporal bones and identified 123 with COM. It is not obvious whether this group included any of the 13 bones previously described by Paparella et al.[9] Many of these 123 cases had suffered complications of their infection, and the reported study concentrated on the middle ear. Twenty-five cases had labyrinthitis, 11 had infiltration of the round window membrane with inflammatory cells, and 22 cochleas had some degree of cochlear hydrops (most without labyrinthitis). It was not clear what the cochlear pathology was in ears with clinically uncomplicated COM. There was no comparison of cochlear histology in the COM ears with that of the opposite ear in the 57 unilateral cases.

Shambaugh[12] in 1979 has mentioned "nonsuppurative labyrinthitis with varying degrees of sensorineural impairment" in his list of complications of otitis media, and Beales[13] maintained that "cochlear degeneration may develop very insidiously in chronic otitis media and should be carefully noted since it discourages any nonessential operative treatment."

A report of association between endolymphatic hydrops and otitis media in a study of 560 temporal bones by Paparella et al[14] noted ten COM bones (nine cases) which had cochlear hydrops. Nine cochleas had slight hydrops in the apical turn, and one had moderate hydrops in the apical turn and profound hydrops in the middle turn. Detailed examination of cochlear structures was not performed although there were said to be some hair cell and ganglion cell losses especially in the basal turn, more so in older patients. The total number of COM bones examined was not stated, unilateral cases were not identified, and it was not obvious whether these bones included those studied by Paparella et al[9] in 1972 or Meyerhoff et al[11] in 1978.

Stewart and Belal[15] studied the round window in human temporal bones. In 56 ears with COM seemingly confined to the middle ear, they found six which had eosinophilic precipitates and occasional round cells within the perilymph on the inner surface of the round window membrane. Five of these ears were from patients who at the time of death had meningitis, which by itself may cause perilymph precipitates due to an increased protein concentration in the cerebrospinal fluid; the remaining ear had a lateral semicircular canal fistula. None of these six ears, all of which belong to the collection of the Massachusetts Eye and Ear Infirmary, were used in this study because of these diagnoses.

In view of the many unanswered questions on the effects of uncomplicated COM on the human cochlea, a two-part study was performed using cases restricted to unilateral COM. This selection removes some of the possible confounding factors by using the normal opposite ear as a control. The first part consists of a retrospective clinical study based on audiometric data; the second is an analysis of temporal bones showing signs of COM.

CLINICAL STUDY

Methods. The medical records of 811 patients attending the Massachusetts Eye and Ear Infirmary from January 1, 1978 to June 30, 1981, with the diagnosis of COM were examined. Of these, 87 patients were identified as having unilateral COM who also satisfied other criteria noted as follows. COM was defined to conform with categories 1 and 3c according to the classification scheme of the Ad Hoc Committee of the American Academy of Otolaryngology on definition and classification of otitis media and otitis media with effusion.[16] This definition excluded patients having otitis media with effusion (category 2) and those with otitis media and perforation at the acute or subacute stages (categories 3a and 3b). Records were also excluded if there were histories of 1) familial deafness, 2) disease in the involved ear other than due to infection, 3) previous ear surgery, 4) systemic ototoxic disease or systemic treatment with ototoxic drugs, 5) vertigo suggestive of labyrinthine disorder or labyrinthitis, 6) a positive fistula test, 7) a labyrinthine fistula or window obstruction later found at surgery,

TABLE 1. AGE DISTRIBUTION AT TIME OF AUDIOMETRY

Age (yr)	*No. of Patients*
0-10	7
11-20	14
21-30	21
31-40	17
41-50	15
51-60	12
61-70	1
Total	87

8) occupational or extraordinary noise exposure, 9) head injury, including traumatic tympanic membrane perforation, and 10) disease in the uninfected ear.

The records were examined to ensure that only those with a normal description of the uninfected tympanic membrane were used, and cases were excluded if audiometry was inadequate. All but nine of the 87 selected patients had surgery on the infected ear during the course of their management, so the most recent adequate audiogram prior to surgery (or the latest audiogram if unoperated) was used in the following data. An adequate audiogram was one which had values (with appropriate masking of the opposite ear) for bone conduction at 500, 1,000, 2,000, and 4,000 Hz in the infected ear, and either bone-conduction or air conduction values for those frequencies in the normal ear. The cases fell into two groups: one group of 29 (one third) where bone conduction values were known for both ears, and another of 58 (two thirds) where bone conduction audiograms for the infected ear had to be compared with air conduction audiograms for the normal ear because bone conduction had not been tested.

Speech discrimination scores were recorded if documented bilaterally (53 cases). Audiograms obtained from audiometers calibrated to the ASA 1951 standard were converted to the ISO 1964 standard; those obtained from ANSI 1969 calibrated audiometers did not require conversion. The audiograms had been recorded by different testers using different audiometers.

The two groups of cases divided according to audiometric assessment were distributed similarly with respect to sex and age. There were 40 men and 47 women. Age at the time of audiometry ranged from 6 to 65 years (Table 1). There were 54 whites, four blacks, and two orientals within these groups, with 27 of unknown ethnic origin. Symptoms of otalgia, otorrhea, vertigo, and tinnitus were reported as in Table 2. The left ear was involved in 37 patients and the right in 50.

The duration of infection ranged from one month to 42 years, although this information was often imprecisely recorded. In 15 cases the duration could not be ascertained; many others could only be assigned within broad spans of years. Therefore duration of infection is reported in groups of years (Table 3). Two cases were recorded as having a one-month period between the onset of symptoms and the time of the audiogram, which strictly speaking, should have placed them in the subacute (3b) category of otitis media (4 to 12 weeks). However, these cases had advanced cholesteatomas which would have been unlikely to develop to this stage within three months, and so have been included as cases of COM.

In the 78 cases that eventually were operated upon it was noted at the time of surgery that 42 (48%) had acquired cholesteatomas while 29 (33%) had simple mucosal inflammation (Table 4). Twenty cases had active ear discharge at the time of audiometry, 48 had not, and in 19 cases it was not specified in the record. The occupations of 78 of the patients were known, and none are normally associated with excessive noise exposure. Topical aminoglycoside ear drops had been prescribed in 31 cases, but in 52 cases information about such treatment was lacking. In only four cases was it clear that antibiotic ear drops had never been used.

TABLE 2. DISTRIBUTION OF OTOLOGICAL SYMPTOMS FROM PATIENTS' HISTORIES

Symptoms	*Present*	*Absent*	*Not Stated*
Otalgia	23 (26%)	32 (37%)	32 (37%)
Otorrhea	72 (83%)	7 (8%)	8 (9%)
Vertigo	14 (16%)	50 (58%)	23 (26%)
Tinnitus	11 (13%)	27 (31%)	49 (56%)

TABLE 3. DISTRIBUTION OF DURATION OF INFECTION

No. of Years	*No. of Patients*
0-10	43
11-20	13
21-30	9
31-42	7
Not stated	15
Total	87

Results. Comparisons of hearing thresholds between normal and COM ears were made within each of the two groups in this study with the two different audiometric methods of assessment and also after the groups were amalgamated into a single group. For each group the hearing in the normal and the infected ears was compared at each of the four frequencies 500, 1,000, 2,000, and 4,000 Hz, and the hypothesis that there was no statistically significant difference between values for each pair was tested by a paired *t* test (Table 5). Probability values throughout this study refer to the probability that a result would have arisen by chance alone. In all 12 situations there was a larger mean threshold for the infected ears as compared to the normal ears. On comparing the bone conduction thresholds for normal ears with bone conduction thresholds for infected ears, the mean differences (4.1, 4.7, 5.5, and 4.7 dB, respectively) were similar for the four frequencies, but comparisons of air conduction thresholds for normal ears with bone conduction thresholds for infected ears gave values that increased with frequency (1.0, 4.1, 8.4, and 9.5 dB, respectively). Combining the two groups still showed an increase with frequency (Table 5 and Fig 1) and they were considered as a single group for the remaining comparisons.

Threshold differences between normal and infected ears were compared for groups with infection of different durations. There was a general trend for a greater difference to appear with greater duration of disease, although individual points deviated from the trend (Fig 2). For this and the following remaining comparisons, the mean values at the four tested frequencies for each patient were calculated and used to test the significance of any difference between normal and COM ears (Fig 3). Analysis of

TABLE 4. DISTRIBUTION OF DISEASE FOUND AT SURGERY

Pathology	*No. of Patients*
Simple mucosal inflammation	29 (33%)
Acquired cholesteatoma	42 (48%)
Congenital cholesteatoma	2 (2%)
Cholesterol granuloma	1 (1%)
Retraction pocket	4 (5%)
Not operated	9 (11%)
Total	87

TABLE 5. DIFFERENCE IN HEARING THRESHOLD BETWEEN NORMAL AND INFECTED EARS

	No. of Patients	*Mean Differences between Normal and COM Ears (dB)*			
		500 Hz	*1,000 Hz*	*2,000 Hz*	*4,000 Hz*
Normal (BC) - COM (BC) 2SE	29	-4.1 ($p > 0.02$) 3.82	-4.7 ($p > 0.02$) 4.38	-5.5 ($p < 0.01$) 3.88	-4.7 ($p > 0.02$) 4.36
Normal (AC) - COM (BC) 2 SE	58	-1.0 ($p > 0.4$) 2.48	-4.1 ($p < 0.01$) 2.54	-8.4 ($p < 0.001$) 2.88	-9.5 ($p < 0.001$) 3.42
Normal (BC or AC) - COM (BC) 2 SE	87	-2.0 ($p > 0.05$) 2.10	-4.3 ($p < 0.001$) 2.22	-7.4 ($p < 0.001$) 2.32	-7.9 ($p < 0.001$) 2.74

BC - Bone conduction; AC - Air conduction.

variance for the groups with infection of different duration gave a variance ratio of $F = 1.32$ (not significant at the 5% point). Mean threshold differences between normal and infected ears are shown in Figure 4 for different age groups. This showed a trend toward greater differences in those of older age groups. Analysis of variance for these groups gave a variance ratio of $F = 3.56$ (significant at the 1% point).

Forty-eight patients had discharge from the infected ear at the time of audiometry, while 20 were reported to have no discharge. The mean hearing differences for the four frequencies were 2.1 dB greater for those that had discharge than for those that had not ($p > 0.3$). An unpaired t test was used for this and the next comparison. Comparison of mean threshold differences for the two commonest types of pathology (acquired cholesteatoma and mucosal disease) showed only a 0.3 dB greater loss for those with mucosal disease ($p > 0.8$). Speech discrimination scores (available in 53 cases) for normal ears were only a mean 1% ($p > 0.1$) better than for infected ears.

HISTOPATHOLOGICAL STUDY

Methods. The collection of temporal bones in the Massachusetts Eye and Ear Infirmary was reviewed for cases of unilateral COM. Of the 1,200 serially sectioned temporal bones there were 33 cases of unilateral COM with the opposite temporal bone available for comparison, together with a clinical history. The same criteria for exclusion from the clinical study were applied to this histopathological study and resulted in a group of 15 pairs of temporal bones left for study. The exclusion of 18 of the cases was for the following reasons: three patients had intracranial tumor (one pontine glioma, one cerebellopontine angle meningioma, one hypothalamic tumor), two diabetes, one labyrinthitis, one possible Menière's disease, one severe otosclerosis with encroachment on the cochlea, one congenital syphilis, one congenital deafness, and one treated with nitrogen mustard. Seven patients excluded had had ear surgery (one cortical, three modified radical, three radical mastoidectomies).

Although one case of severe otosclerosis was excluded from the study, two with mild histological otosclerosis were included. One patient had foci in the footplates of the stapes in both normal and infected ears, and one had separate foci anterior to the oval window and in the cochleariform process on the infected side; neither patient had stapes fixation or cochlear endosteal involvement. These cases were included because there is evidence to indicate that only when the stapes is fixed and the endosteum of the cochlea is involved is there damage to the inner ear.[17]

In three cases the "normal" middle ears had minimal mucosal changes which indicated a resolved acute otitis media in the past, a condition which was suggested by the patients' histories of childhood symptoms in two cases, but not in the third. One case also had otosclerosis involving the cochlear endosteum of the "normal" ear only. These three cases were included in the general study because they showed little evidence of previous infection in the "normal" middle ear, and the one with otosclerosis only involved

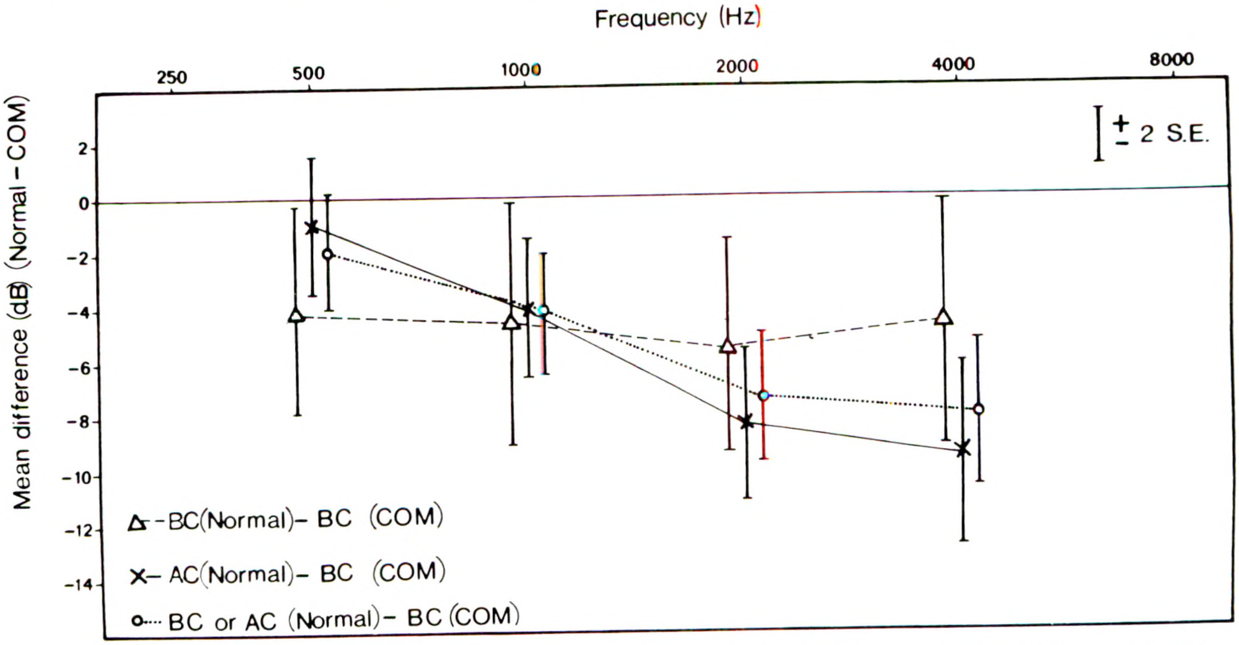


Fig 1. Graph of mean differences (dB) between normal and COM ears plotted against frequency for different parameters of assessing hearing in normal ears.

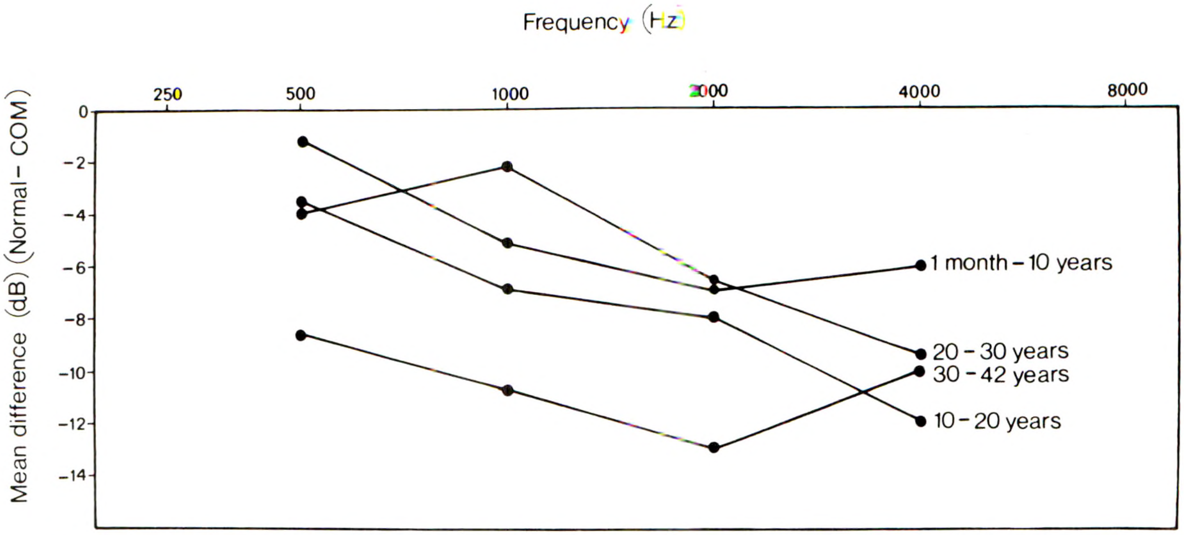


Fig 2. Graph of mean differences (dB) between normal and COM ears plotted against frequency for different periods of duration of infection.

the "normal" ear. Because their inclusion in the main group of cases would introduce confounding factors, they are described separately from the main data.

There remained 12 cases of unilateral COM where the cochlea of the infected ear could reasonably be compared to that of the other side. Any effects of presbycusis might presumably be balanced by similar pathology present in the normal ear.

The temporal bones had been prepared in the routine manner by decalcification and embedding in celloidin. Serial horizontal sections were cut at a thickness of 20 μm and every tenth section was mounted and stained with hematoxylin and eosin for examination by light microscopy.[18]

The cochleas of each pair of ears were serially reconstructed graphically as described by Guild[19] and Schuknecht.[20] The length of the organ of Corti along the junction of the inner and outer pillar cells was measured from the base, and divided into 1-mm segments. Counts of inner and outer hair cells were made in each of the approximately 100 places where the cochlea was sampled along its length, and the percentages of hair cells missing per millimeter were calculated. The hair cells were examined by 450x dry magnification, and a missing hair cell was determined by the absence of a nucleus in the expected area of the organ of Corti. Any areas where the whole organ of Corti was missing from the basilar membrane were also recorded. The accuracy of estimation of percentage loss of hair cells per millimeter varied with the number of samples which were present from each millimeter. Cuts perpendicular to the organ of Corti allowed up to five samples per millimeter, whereas tangential cuts sometimes only gave one sample for estimation of loss. Occasionally a millimeter in the basal turn had no samples present. Segments of organ of Corti which had similar numbers of sample estimations were approximately the same in each ear at the base, but did not correspond so well progressively toward the apices. Whereas assessment of hair cell loss could be made up to the very apex of the cochlea, this could not be done in the first 2 mm of the basal hook region because horizontal sectioning of the temporal bone gives sections in this area where the supporting Deiters' cells are superimposed on hair cells, making hair cell assessment unreliable unless both supporting cells and hair cells are completely missing. On the same cochlear reconstructions the stria vascularis was assessed by the percentage (10% decrements) of bare epithelium overlying the spiral ligament with absence of the normal specialized strial epithelial cells. The same varying number of samples per millimeter applied as for the hair cells, and the error of this visual assessment was considered to be about 10%.

The spiral ganglion was reconstructed in a similar manner. The center of Rosenthal's canal where cochlear neurons are normally most dense was used as the reference for the reconstruction. The spiral ganglion was divided into four segments (I-IV) as described by Otte,[21] and counts of spiral ganglion cells were made in each of the approximately 30 places where the spiral was sampled. Cells were counted at 450x dry magnification, and only ganglion cells which had a visible nucleus considered to be greater than one third the normal nuclear diameter were counted. Samples of type I spiral ganglion cells[22] were measured and found to have a mean nuclear diameter of eight μm. In estimating total numbers of ganglion cells the actual counts need to be multiplied by ten because only every tenth section was examined. A correction factor was then applied to correct for the error due to double counting of cells which have had their nuclei split by sectioning and so would be represented on two adjacent sections. The formula of Murphy (quoted by Konigsmark[23]) was used to calculate this factor:

$$N = n \frac{t}{t + 2\sqrt{r^2 - (\frac{k}{2})^2}} = 0.77\ n$$

where N = the estimated number of neurons, n = counted number, t = section thickness (20 μm), r = radius of nucleus (4 μm), and k = maximum diameter of uncounted fragments (empirically taken as one-third diameter of the nucleus). The actual counts were therefore in effect multiplied by 7.7 to correct for double counting of nuclei and for the sections not examined. The

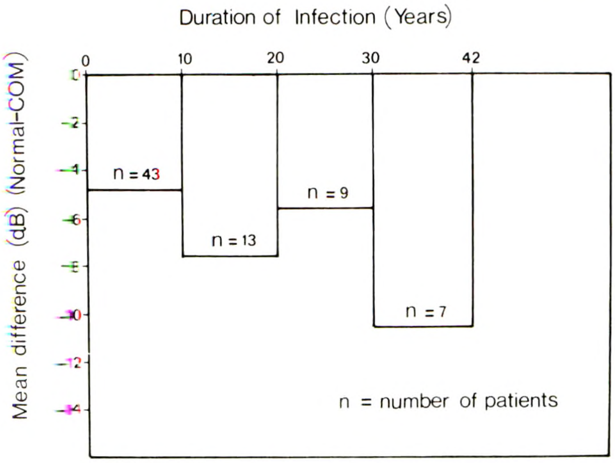


Fig 3. Histogram showing mean differences (dB) between normal and COM ears (using the mean of hearing threshold at 500, 1,000, 2,000, and 4,000 Hz in each ear) for different periods of duration of infection.

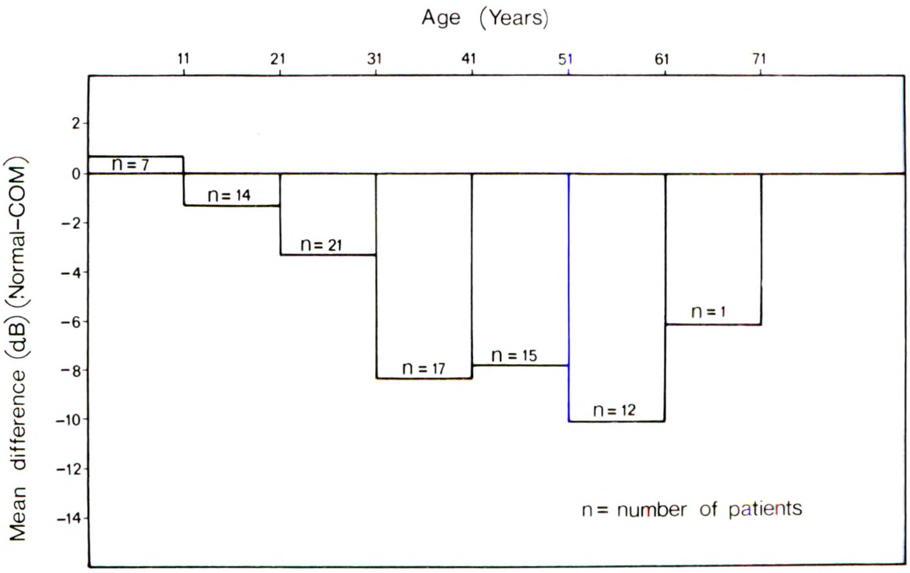


Fig 4. Histogram showing mean differences (dB) between normal and COM ears (using the mean of hearing threshold at 500, 1,000, 2,000, and 4,000 Hz in each ear) for different age groups.

accuracy of the counts would have been improved by counting nucleoli, as the smaller the particle counted, the less the error of overcounting due to splitting of particles. A number of the temporal bones had basophilic staining of the nucleus which was too dense to reliably identify the nucleolus, so it was decided to use the presence of the nucleus as the criterion for counting a ganglion cell in all cases. Both type I and II cells were counted, but as type II cells make up such a small proportion of the total,[22] the error of the different size of nucleus was not considered in calculating the correction factor.

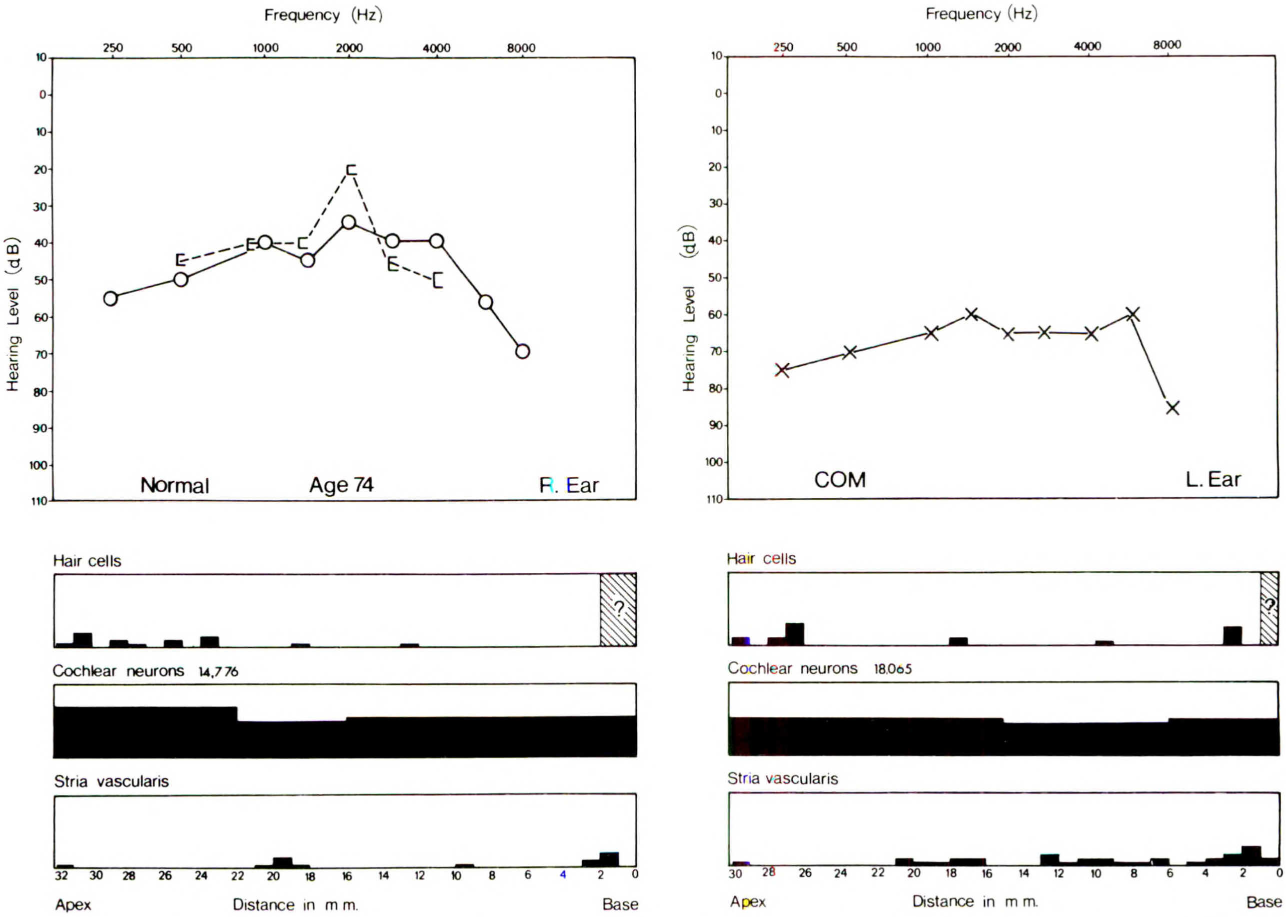


Fig 5. (Case 1) This patient had a perforation of the left tympanic membrane for an unknown duration. She died of myocardial infarction at age 77. There was no histopathology in the right middle ear. The left ear had a posteroinferior perforation with the residual tympanic membrane thickened with hyalin plaques. There was partial epidermization of the middle ear including the round window niche, and partial resorption of the tip of the long process of incus. The percentage loss of hair cells, cochlear neurons, and stria vascularis are shown in black with the shaded areas at the base representing regions where assessment of loss could not be made.

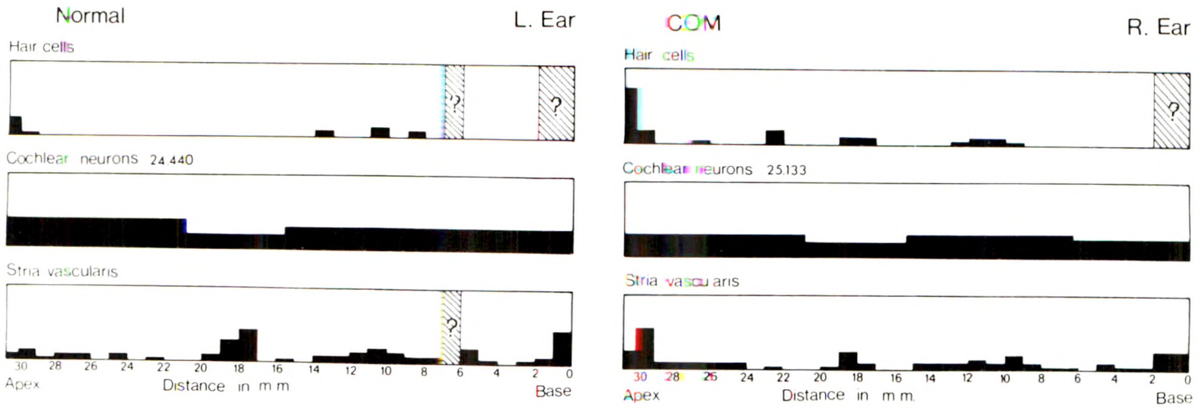


Fig 6. (Case 2) This patient had no ear complaints, had not had an audiogram, and died at age 69 of an adenocarcinoma of the colon. A routine medical examination noted scarred tympanic membranes. Histology showed only a lax tympanic membrane and no middle ear pathology in the left ear. In the sections available no hair cells or stria vascularis were represented from the seventh millimeter. The right tympanic membrane contained tympanosclerosis and there was a posterosuperior retraction pocket with partial erosion of the long process of incus. There were inflammatory polymorphonuclear cells in the middle ear.

The counting was done using an ocular grid, and the error in this method was estimated to be about 2% by recounting sections. The counts were converted to percentages of normal by using the data of Otte et al[24] for "young subjects."

Cytocochleograms and audiograms for the 15 cases appear in Figures 5 to 19.

Audiometry was available for six of the 12 cases, but only four had data comparable to that in the clinical study, and although the numbers are too small for reliable analysis, the previously noted trend of an increase in bone conduction thresholds in the infected ears was seen (Figs 7-9 and 16).

There were five men and seven women with ages at death ranging from 33 to 87 years. Cause of death was reported as myocardial infarction (four), cardiac failure (three), cardiac arrest

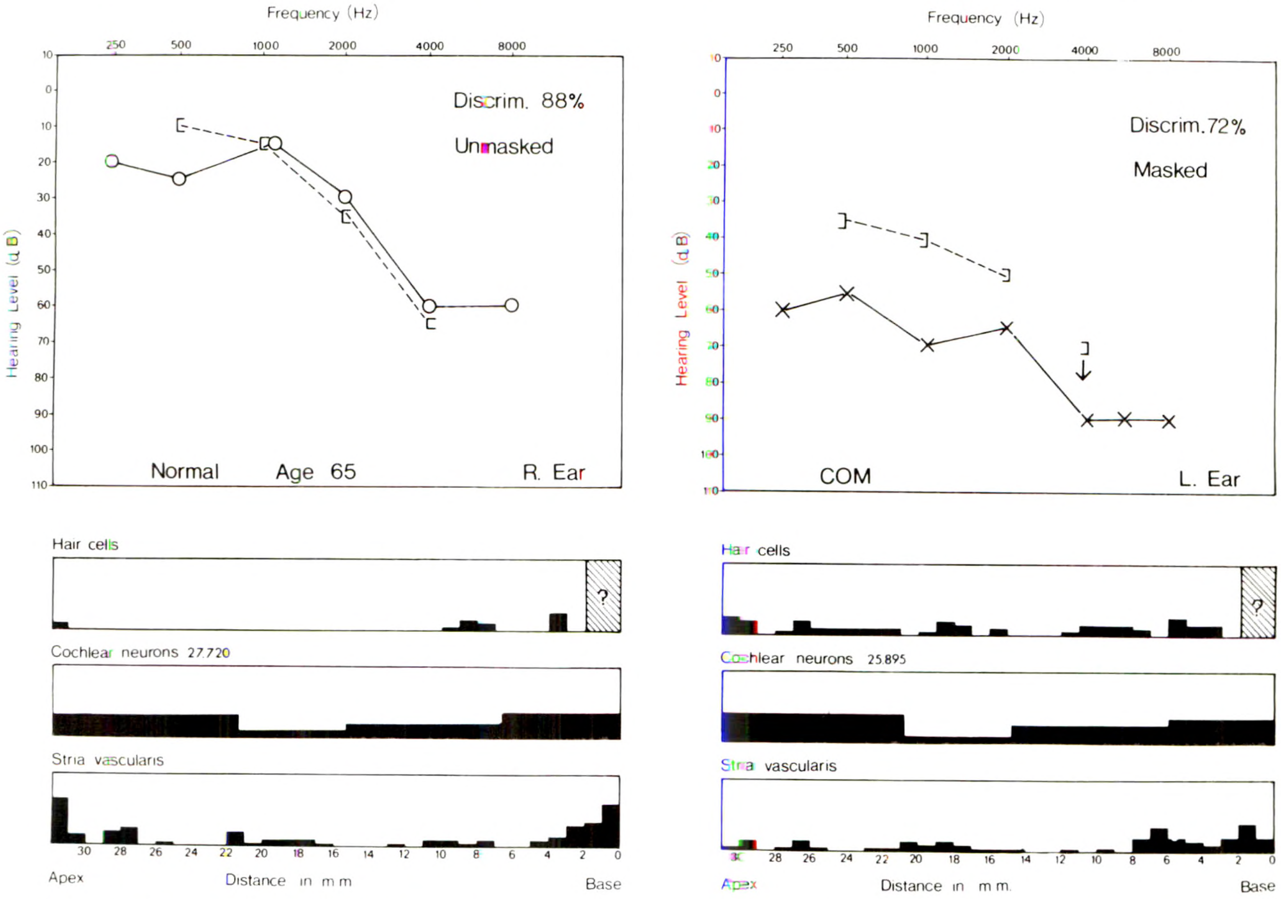


Fig 7. (Case 3) This 65-year-old man complained only of bilateral tinnitus. Otological examination was reported as "normal right tympanic membrane, retracted and nonmobile on the left." Three months later after audiometry he died of a bronchoalveolar carcinoma. There was no histopathology in the right middle ear. In the left ear the tympanic membrane was missing and there was partial fibro-osseous obliteration of the hypotympanum and mesotympanum, fixing the malleus and incus. The mastoid was obliterated. The long process of incus and stapes superstructure were missing.

TABLE 6. COMPARISON OF COCHLEAR FINDINGS IN NORMAL AND COM EARS

Case No.	*Ears*	*Compression Artifact*	*Endolymphatic Hydrops*	*Eosinophilic Precipitate* *Scala Tympani*	*Scala Media*	*Scala Vestibuli*
1	R Normal	Mild	—	+	—	+
	L COM	Mild	—	+	—	+
2	L Normal	—	—	+	—	—
	R COM	Mild	—	+	—	+
3	R Normal	—	—	—	—	—
	L COM	Mild	—	+	—	—
4	R Normal	—	—	+	—	+
	L COM	Mild	—	—	—	+
5	L Normal	—	—	+	—	+
	R COM	Moderate	—	+	—	+
6	L Normal	Mild	—	—	—	—
	R COM	—	—	—	—	+
7	L Normal	—	Apical 1 mm	—	—	—
	R COM	Mild	—	Few RBCs	—	—
8	R Normal	—	Generalized	—	—	+
	L COM	Mild	Apical 1 mm	—	—	—
9	L Normal	—	Apical 1 mm	—	—	+
	R COM	—	—	—	—	+
10	L Normal	—	Apical 1 mm	—	—	—
	R COM	—	—	+	—	+
11	R Normal	Mild	Generalized	—	—	—
	L COM	—	Apical 1 mm	—	—	—
12	R Normal	—	—	—	—	—
	L COM	Mild	Apical 1 mm	—	—	—
13	L Mildly abnormal	Mild	Apical 1 mm	+	—	—
	R COM	Mild	Apical 1 mm	+	+	+
14	L Mildly abnormal	Mild	—	+	—	+
	R COM	—	—	+ +	+	+ +
15	R Mildly abnormal	Mild	—	—	—	—
	L COM	Mild	—	—	—	—

(one), carcinoma of colon, lung, or breast (one each), and temporal lobe abscess (one). The right ear was infected in seven cases and the left in five. The duration of infection was as uncertain as in the clinical study, but was said to be 22 years in one case, greater than three and 19 years in two cases, about 60 and 65 years in two cases, and unknown in the remaining seven cases. The time from death to fixation of 11 of the pairs of temporal bones ranged from 2 to 24 hours, being unstated in one case.

There was little postmortem autolysis in the 24 temporal bones and only a mild degree of compression artifact (three normal, eight COM), characterized by Reissner's membrane lying partly on the organ of Corti. In only one bone (Fig 9, case 5) did this artifact preclude detailed assessment of hair cell loss (Table 5).

The most obvious pathology in the infected ears was perforation of the tympanic membrane and epidermization of the middle ear (five), cholesteatoma (two), mucosal disease with perforation (one), retraction pocket (one), tympanosclerosis of the tympanic membrane and adhesions in the middle ear (one), replacement tympanic membrane with adhesions (one), and fibrosis in the middle ear (one). The round window niches of the infected ears were examined, and in three cases they were normal, containing only mucosal folds and eosinophilic fluid. Five had fibrous tissue in the niche (containing dark pigment in three), two had inflammatory tissue, one had squamous epithelium lining the niche, and one had a basophilic deposit in the submucosa with hyalinization of the round window membrane. In the normal ears, nine of the niches were normal, one had hypertrophied mucosa with the dark pigment present, one contained fibrous tissue, and one had normal mucosal folds but pigment was present in the submucosa.

Results. The cochleas were examined and two of the normal ears had a moderate degree of generalized endolymphatic hydrops, while three each of the normal and infected ears had physiological hydrops[25] of the most apical 1 mm (Table 6). The degree of spiral ligament atrophy was comparable in each pair of ears and consistent with the normal aging process. There were no abnormalities noted in the tectorial membranes. The cochlear structures were examined for signs of inflammation. All ears, normal and infected, had a few round mononuclear cells on the scala tympani side of the round window membrane. These did not resemble polymorphonucleocytes, lymphocytes or macrophages. There was some eosinophilic precipitate lining the margins of the scala tympani in four of the normal ears and five of the infected ears. The scalas media of the 12 pairs were clear of any precipitate. In the scalae vestibuli there were precipitates present in five of the normal ears and in seven of the infected ears (Table 6).

The percentage loss of hair cells, stria vascularis, and cochlear neurons for each pair of ears is shown in black in the cytocochleograms (Figs 5-16) with shading used in the regions where assessment was not possible. Audiograms, where they are available, are plotted according to Schuknecht's[26] modification of the Koenig[27] scale whereby frequencies below 500 Hz are plotted arithmetically and those above 500 Hz on a logarithmic scale. On visual inspection there was no obvious greater loss of the specialized cochlear structures in the infected ears, so the data were analyzed in detail.

Comparison was made of hair cell losses between infected and normal ears in the 11 pairs of ears in which hair cell counts were possible. Small losses of hair cells were scattered throughout the length of the organ of Corti. To test whether there was any

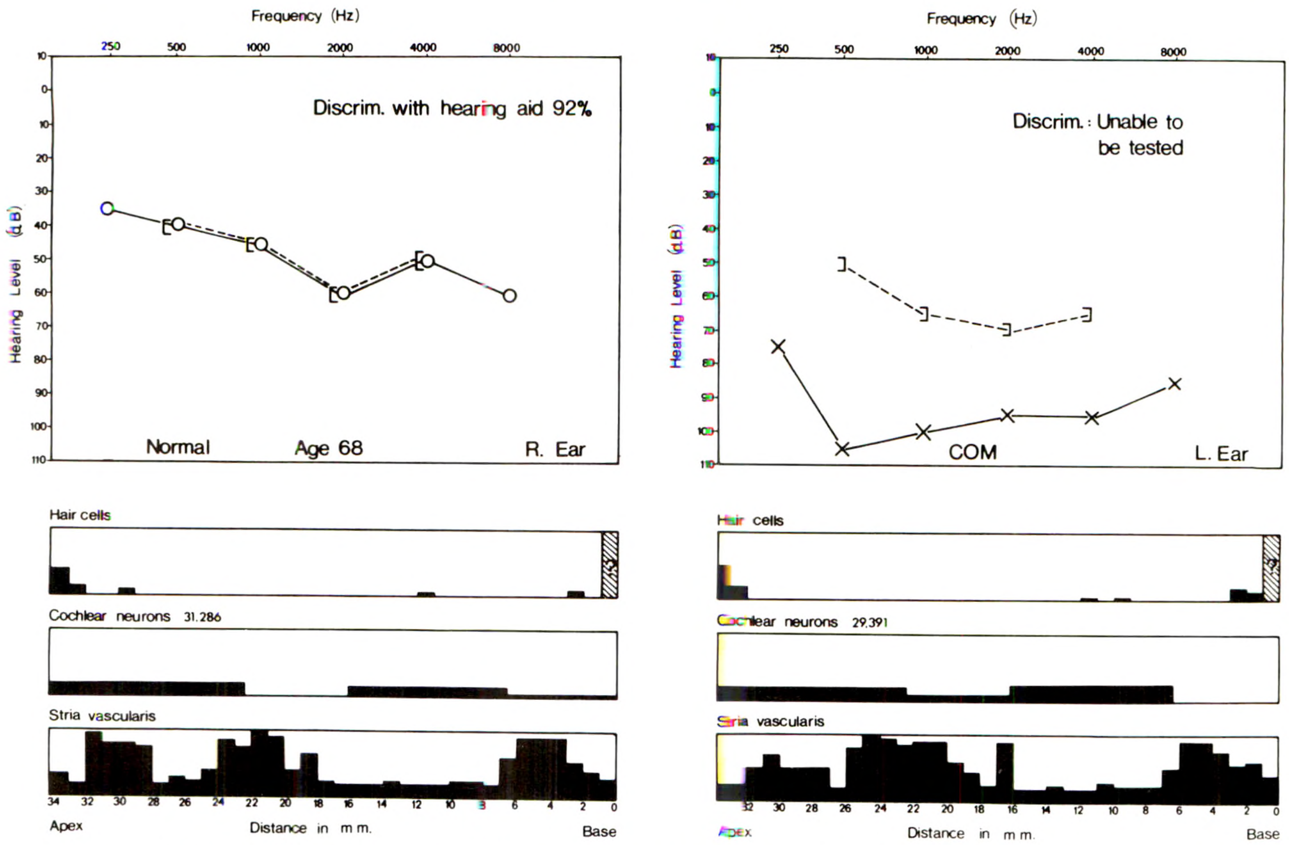


Fig 8. (Case 4) This woman had a "scarred and retracted left tympanic membrane" 19 years prior to death. She wore a hearing aid in the right ear and died of a myocardial infarction at age 72. There was no histopathology in the right middle ear but there were separate foci of otosclerosis anterior to the oval window and in the cochleariform process, not fixing the stapes or involving the cochlear endosteum. The left tympanic membrane was missing and there was epidermization of the middle ear. There was fibrocystic sclerosis in the mesotympanum and scattered tympanosclerosis. The long process of incus and stapes superstructure were absent. The manubrium of the malleus was displaced medially and was adherent to the promontory. There was fibrocystic and osseous sclerosis of the mastoid.

statistical difference in this loss between normal and infected ears, comparisons were made in three ways:

1. For the most basal eight individual millimeters, where there were data for each pair of ears, comparisons were made. Although greater mean percentage losses were present in the fifth and sixth millimeters of the infected ears (3.6% [$p>0.1$], 2.3% [$p>0.3$], respectively), there was greater loss in the normal ears in the third and fourth millimeters (6.5% [$p>0.4$], 9.1% [$p>0.1$], respectively) which are closer to the round window. As previously explained, hair cell losses could not usually be estimated in the first and second millimeters; there were no differences in losses in the seventh and eighth millimeters.
2. The mean percentage losses of hair cells for the six most apical complete millimeters of the normal and infected ears were compared. There was a 0.5% ($p>0.8$) greater loss in the normal ears.
3. The mean percentage losses of hair cells per millimeter throughout the length of the cochlea were calculated where paired data were available for the 11 pairs of ears. Unpaired millimeters due to lack of data or different lengths of cochleas were excluded. There was a trivial 0.003% greater loss of hair cells in the infected ears.

Similar comparisons were made between degrees of strial atrophy in the 12 pairs of normal and infected ears. The mean percentage of strial atrophy corresponding to the first 6 mm of the organ of Corti of each ear was 1.7% ($p>0.3$) greater in the infected ears. Comparison for the most apical 6 mm showed 3.2% ($p>0.3$) greater mean loss in the normal ears. The mean percentage strial atrophy for the basal 29 mm was calculated in 11 of the pairs of ears. Data were incomplete for the remaining pair (Fig 6, case 2). Mean atrophy was 1% greater ($p>0.3$) in the normal ears. There were basophilic strial deposits in seven of the normal ears and eight of the infected ears.

Comparison of the total neuronal counts in the 12 pairs of ears showed a mean for the normal ears of 956 cells greater than on the infected side ($p>0.1$). An estimation was made of the percentage length of the organ of Corti served by each of the four segments (I-IV) for the normal and infected ears, assuming a strictly radial relationship between spiral

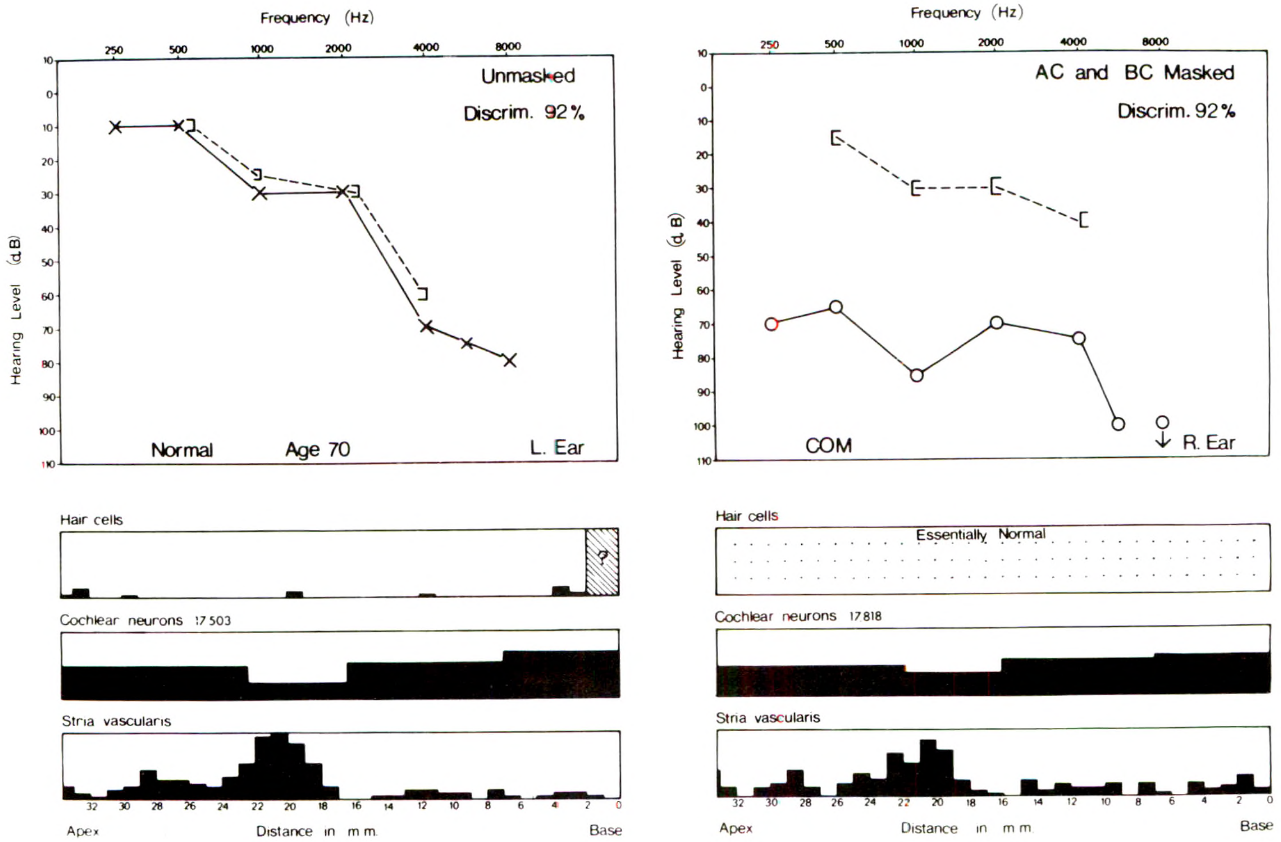


Fig 9. (Case 5) This patient had recurrent right otorrhea and hearing loss beginning in childhood. Examination at age 69 reported mucoid discharge from a large perforation in the right ear. He died at age 71 of a myocardial infarction. There was no histopathology in the left middle ear. A large perforation was present in the right tympanic membrane with partial epidermization of the middle ear. The submucosa was thickened and there were inflammatory polymorphonuclear cells present. There was loss of part of the manubrium of the malleus and body of the incus, and absence of the long process. The epitympanum, antrum, and mastoid had fibrous obliteration. The bony external ear canal was partially eroded posteriorly. Compression artifact prevented detailed counting of hair cells in the right ear.

ganglion cells and hair cells. The different lengths of the organ of Corti in each pair of bones make absolute lengths not suitable for comparison, so percentages of total length were used. The greatest percentage difference in length of the organ of Corti supplied by any comparable pair of segments (48 pairs) was 2.6%. This variation was thought small enough to allow comparison of the individual segments I-IV in the normal and infected ears, and resulted in a greater mean number of cells in segment III of the normal ears (55 cells [$p>0.7$]) and a greater mean number of cells in segments I, II, and IV of the infected ears (230 [$p>0.2$], 390 [$p>0.1$], and 392 [$p>0.1$], respectively). Thus it seems that there is no evidence that the infected ear has fewer hair cells or ganglion cells than the normal ear.

The three pairs of bones with the possibility of infection in the normal ear were analyzed in the same way as the previously described 12 pairs (Figs 17-19 and Table 6), and they also demonstrated no greater abnormalities in the infected ears as compared to the nearly normal ears. Two of these cases had eosinophilic precipitates in the scala media of the COM ear only, in each case in combination with precipitate in the scalae tympani and vestibuli (Table 6).

DISCUSSION

The clinical study of the effect of COM on the cochlea was complicated by the different parameters used to assess inner ear function in the normal ear. Use of the two methods of assessment gave different results. Although an increased threshold of hearing was observed in both cases at each frequency, by using bone conduction in the normal ear this was uniformly around 5 dB. Use of air conduction in the normal ear gave increased thresholds (1 to 9.5 dB) rising with frequency. At 1,000, 2,000, and 4,000 Hz this increased threshold was statistically (at the probability level $p<0.01$) most unlikely to have arisen by chance in the cases where air conduction was used in the normal ear, whereas only at 2,000 Hz was this true in the cases where bone conduction had been tested in the normal ear. When the two groups were combined, this significantly increased threshold was still evident at 1,000, 2,000, and 4,000 Hz (Table 5).

A comparison was also made between the two

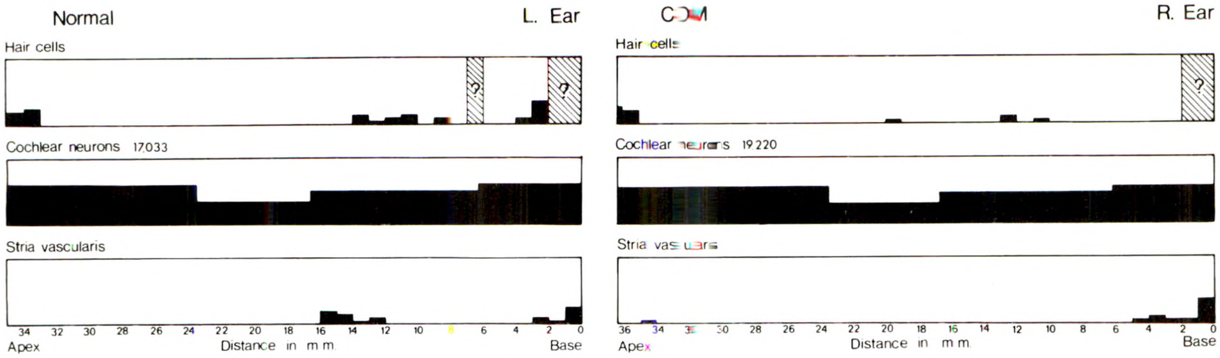


Fig 10. (Case 6) This patient complained of hearing loss at age 65, but no otologic studies were performed. He died of a myocardial infarction at age 67. There was no histopathology in the left middle ear. In the serial sections available no hair cells were represented from the seventh millimeter. In the right ear a small cholesteatoma extended into the middle ear from the posterosuperior quadrant of the tympanic membrane. There was absence of the long process of incus. The mastoid was sclerotic.

groups at each frequency, and they were not found significantly different, the greatest difference being at 4,000 Hz ($p>0.05$). It had initially been surmised that use of air conduction in an apparently normal ear would have been an acceptable approximation to bone conduction, because if there was a small concealed conductive loss, the true bone conduction threshold would have been lower, so that any threshold difference between normal and COM ears should have only been reduced by this error and not exaggerated. If this theory were true, the results by use of air conduction should have been smaller than by using bone conduction; however, this was only the case at 500 and 1,000 Hz, whereas for 2,000 and 4,000 Hz they were larger (Fig 1). Examination of the data gives a possible explanation for the different results. The practice of the Audiology Department at the Massachusetts Eye and Ear Infirmary is normally not to test bone conduction in a seemingly normal ear unless the air conduction tests give abnormal results. The air conduction group was then largely composed of cases where the audiologist assumed from the air conduction tests that the ear was normal, whereas the group which had the bone conduction tests were usually ones where the air conduction thresholds showed small elevations. Thus there is a possibility that although all "normal" ears were by history and examination normal, there may have been some unknown abnormality in "normal" ears tested by bone conduction, which might have reduced any difference between the normal and COM ears. Because neither group could be shown to be the more appropriate for assessing inner ear function, for further evaluation of the data the two groups had been combined. The finding of thresholds increasing with frequency are similar to but smaller than those found by Paparella et al.[8]

Duration of infection apparently had less clear association with threshold differences than did age at the time of audiometry. With increasing age these mean-threshold differences increased significantly. The age data could be accurately determined, whereas the duration of infection was frequently based on a vague subjective opinion, and it may be that a better correlation of duration of infection with threshold differences would have been found with more accurate data. The presence of ear discharge at the time of audiometry and the type of pathology found did not significantly affect the degree of threshold difference found. Speech discrimination scores were not significantly affected by infection.

Although patients with any history of excessive noise exposure were omitted from this study, acoustic trauma due to socioacusis could not be excluded. This would normally be a bilateral effect, but in an infected ear with a conductive hearing loss the cochlea could be partly protected from such sound and sustain less damage than the normal ear. Another asymmetrical effect which could not be controlled was the potential ototoxicity of topical aminoglycoside ear drops. It was not stated in many cases whether the patients had ever been treated with them, but so common is their use that it is likely that most of the cases of COM had been so treated at some stage. In this situation probably only the cochlea of the infected ear was at risk of damage. The effect of both these factors on the results of this study is unknown.

The finding of a threshold difference between normal and infected ears requires an explanation of what might be causing it. It is well known that bone conduction is not synonymous with cochlear function. Although dysfunction in the cochlea might be due to the products of infection destroying sensorineural structures, there are at least three other possibilities. Carhart[4] and Tonndorf[28] have shown that alterations of middle ear structures affect bone conduction thresholds, and it would be expected that middle ear changes occurring in COM could do the same. It has also been speculated that the infection could have an effect on cochlear mechanics by al-

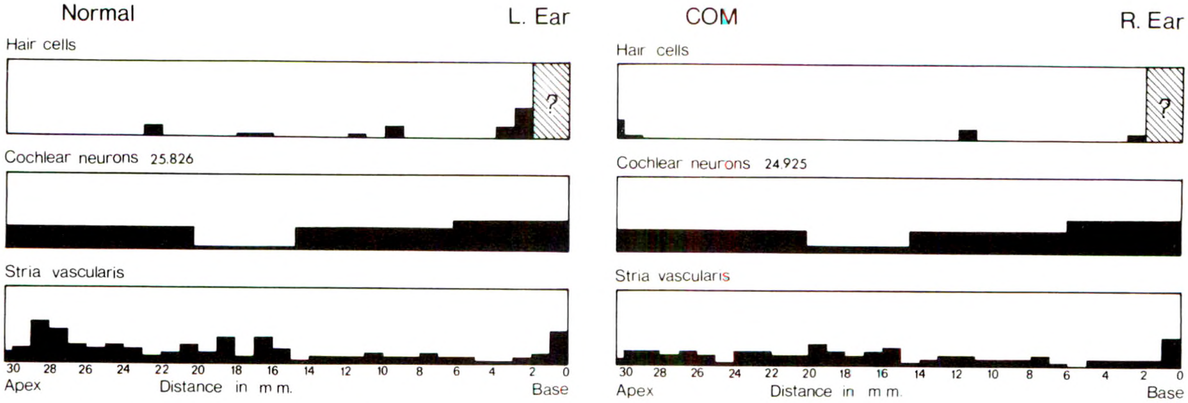


Fig 11. (Case 7) This woman had no otologic complaints and was said to have normal tympanic membranes one month prior to death. The Rinne test was positive bilaterally and the Weber test was lateralized to the right ear. No audiometry was done. She died of cardiac failure at age 49. There was no histopathology in the left middle ear. The tympanic membrane on the right was intact but thickened superiorly with tympanosclerosis, and inferiorly a replacement membrane was present. Anteriorly there was an agonal hemorrhage. Fibrous adhesions were present in the middle ear.

teration of the constituents of the cochlear fluids or by altering the stiffness of the cochlear partition without direct damage to sensorineural structures. Schuknecht[26] considered that the similarity of the pattern of hearing loss in COM to that encountered in some patients with Paget's disease or otosclerosis suggested a similar basic origin, and he hypothesized that a local toxic effect due to each disease process might accelerate the atrophic changes which normally occur in the supporting tissues of the cochlear duct. These changes could possibly alter the mass, stiffness, or friction of the spiral ligament or basilar membrane, and result in altered displacement of the cochlear partition in response to sound. Finally, it is clearly possible for functional changes to occur in sensorineural elements in the cochlea without their disappearance. It cannot be ascertained from this clinical study whether, or to what degree, the hearing threshold increases in the COM ears were caused by each of these four possible components.

The histopathological study offers some data on the effect of infection on the sensorineural structures in the cochlea. On comparison of all the pairs of temporal bones, no consistent difference in hair cell loss was noted between the normal and COM ears. There was scattered loss of hair cells in the cochleas of the COM ears but also in the normal ears, and this illustrates the importance of comparison with the opposite normal ear, which is the best control. No difference in hair cell losses were found at the base, apex, or on average throughout the cochleas. Estimation of differences in the basal hook regions of the cochleas was complicated by the lack of information on hair cells in the most basal 2 mm as explained earlier. This region responds to frequencies above approximately 16,000 Hz, and any differences here in hair cell loss could not be determined in this study. Destruction of hair cells, if it had occurred in this region, would not account for the observed changes in hearing threshold recorded up to 4,000 Hz in the clinical part of the study. This

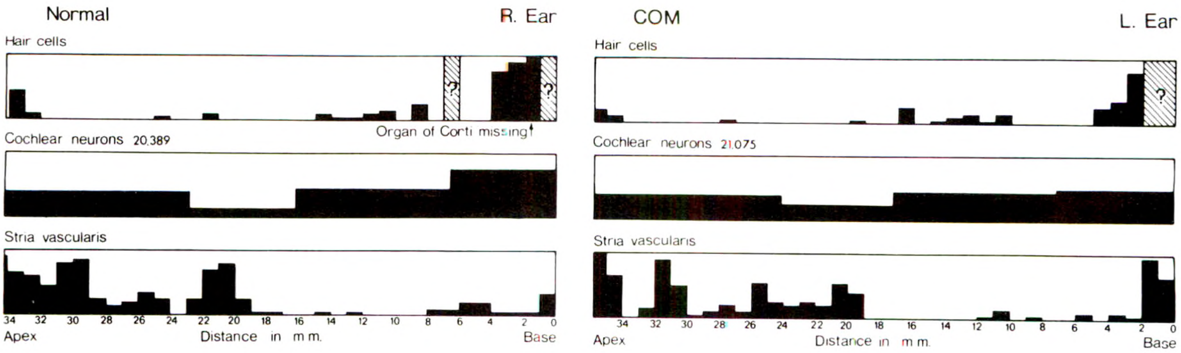


Fig 12. (Case 8) This patient gave a history of discharge from the left ear, but no further details are known. Routine examination reported an opaque left tympanic membrane at age 81. At age 86 she was noted to have a hearing loss. The Rinne test was negative on the left and positive on the right, and the Weber test lateralized to the left ear. No audiometry was done, and she died of cardiac failure at age 86. Histology showed only slight thickening and retraction of the posterosuperior quadrant of the right tympanic membrane and no middle ear pathology. The organ of Corti was completely missing in the second and half of the third millimeters, and in the serial sections available no hair cells were represented from the seventh millimeter. There was absence of the tympanic membrane in the left ear with epidermization over fibrous tissue in the mesotympanum. The malleus and incus were eroded and the stapes was embedded in fibrous tissue. The mastoid contained fibrous tissue and hypertrophied mucous glands.

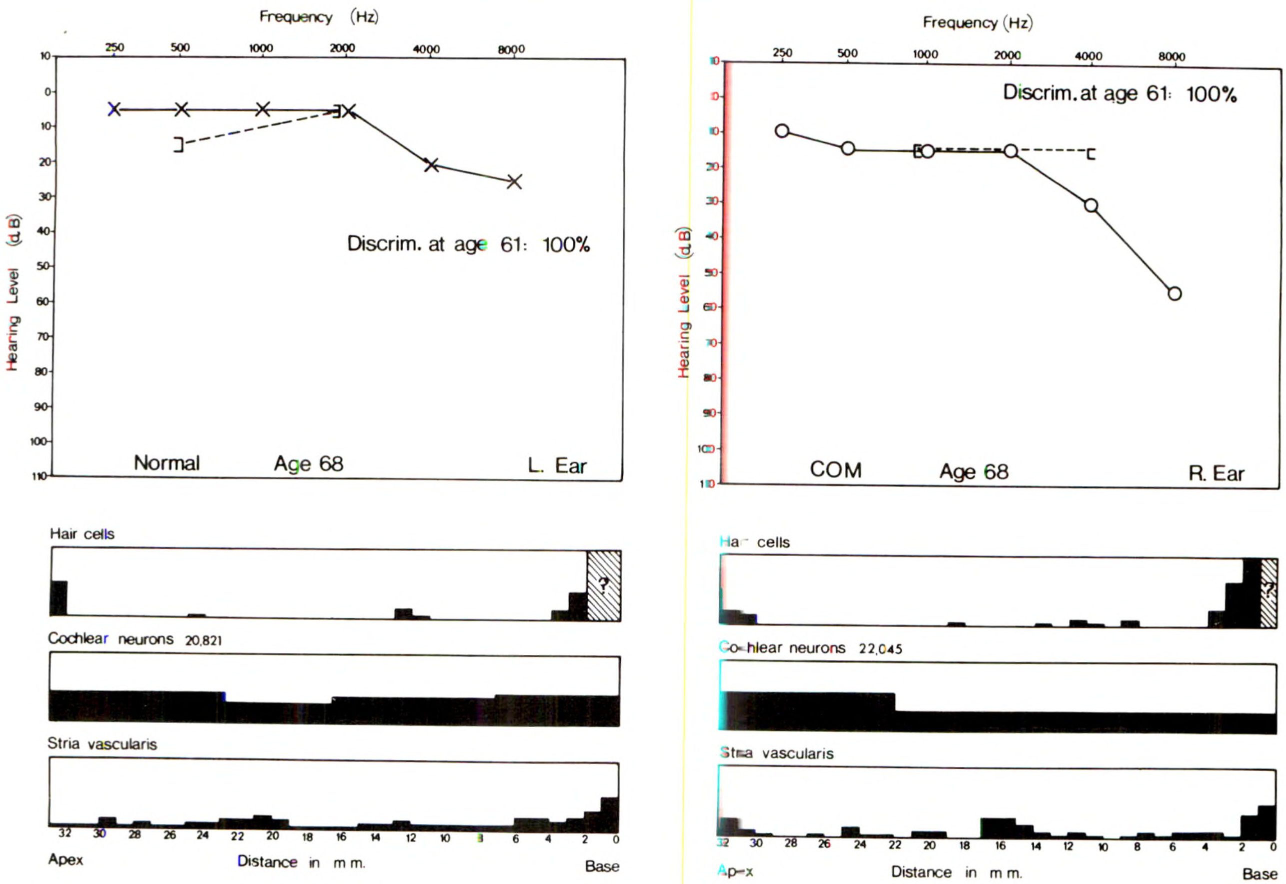


Fig 13. (Case 9) This patient had a right acute purulent otitis media at age 55 with tinnitus and hearing loss, followed by three documented exacerbations over the next 13 years. He died at age 77 of a cardiac arrest. There was no histopathology in the left middle ear. The right tympanic membrane was intact, thickened superiorly, and with a replacement membrane inferiorly. There were adhesions in the middle ear and fibrous articulation of the malleus head with the anterior attic wall.

frequency is represented approximately 10 to 11 mm from the base.

It has been suggested that COM causes sensorineural hearing loss by producing toxins which cross the round window membrane and damage hair cells in the lower basal turn of the cochlea.[9] This study found no evidence that the chronically infected middle ear in the human had caused hair cell destruction. It may be that hair cells had been functionally damaged or had suffered injury to their

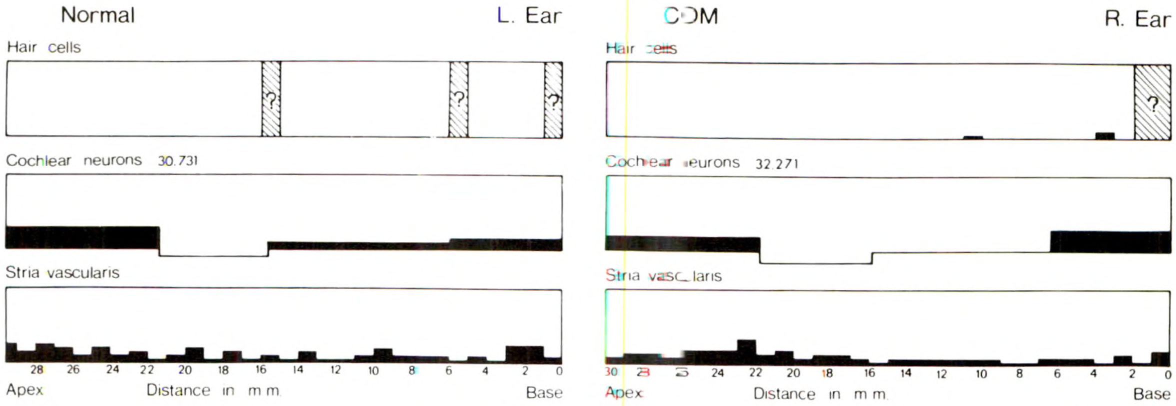


Fig 14. (Case 10) This patient was mentally retarded with no history of hearing loss. At age 33 she complained of severe headache and gave a history of intermittent pain and discharge from the right ear for three years. No audiometry was performed. She lapsed into coma and died the same day. Autopsy revealed a right temporal lobe abscess but no meningitis. There was no histopathology in the left middle ear. In the serial sections available no hair cells were represented from the sixth or 16th millimeters. The right ear contained a cholesteatoma arising from the posterosuperior quadrant of the tympanic membrane extending into the mastoid. There were granulation tissue and polymorphonuclear cells in the middle ear. The long process of incus was absent. No track of infection was seen between the cholesteatoma and the middle cranial fossa, possibly because sections were not obtained far enough superiorly. The cochlear neuronal counts in segment III of each ear were greater than normal.

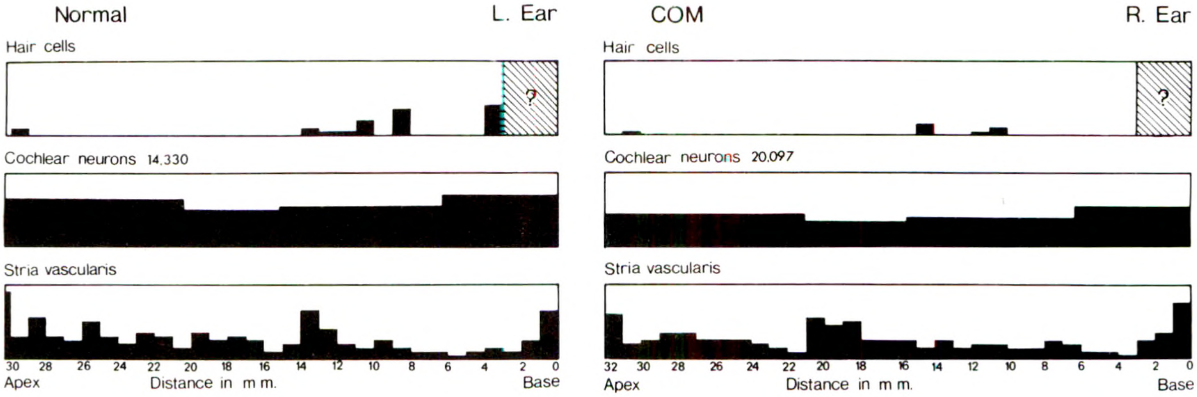


Fig 15. (Case 11) This woman suffered from progressive senile dementia and hearing loss. Otoscopic examination was negative and no audiometry was performed. At age 87 she was noted to be very deaf, but shouting provoked an appropriate answer half the time. She died of cardiac failure at age 87. On histology there was otosclerosis confined to the footplates of both stapes without fixation, otherwise the left middle ear was normal. The right tympanic membrane was intact with fibrous tissue in the middle ear, especially around the stapes, and in the periantral mastoid cells.

stereocilia; at the light microscopic level these changes would not be apparent in human material.

Comparison of stria vascularis atrophy and spiral ganglion cell loss between each pair of ears showed minimal differences at either end or throughout the lengths of the cochleas. The generally symmetrical nature of hair cell and neuronal loss and strial atrophy in each pair of ears is consistent with these changes being due to presbycusis or at least to an agent that acts bilaterally.

The finding of eosinophilic precipitate within the cochlear fluids has been cited by Paparella et al[9] as

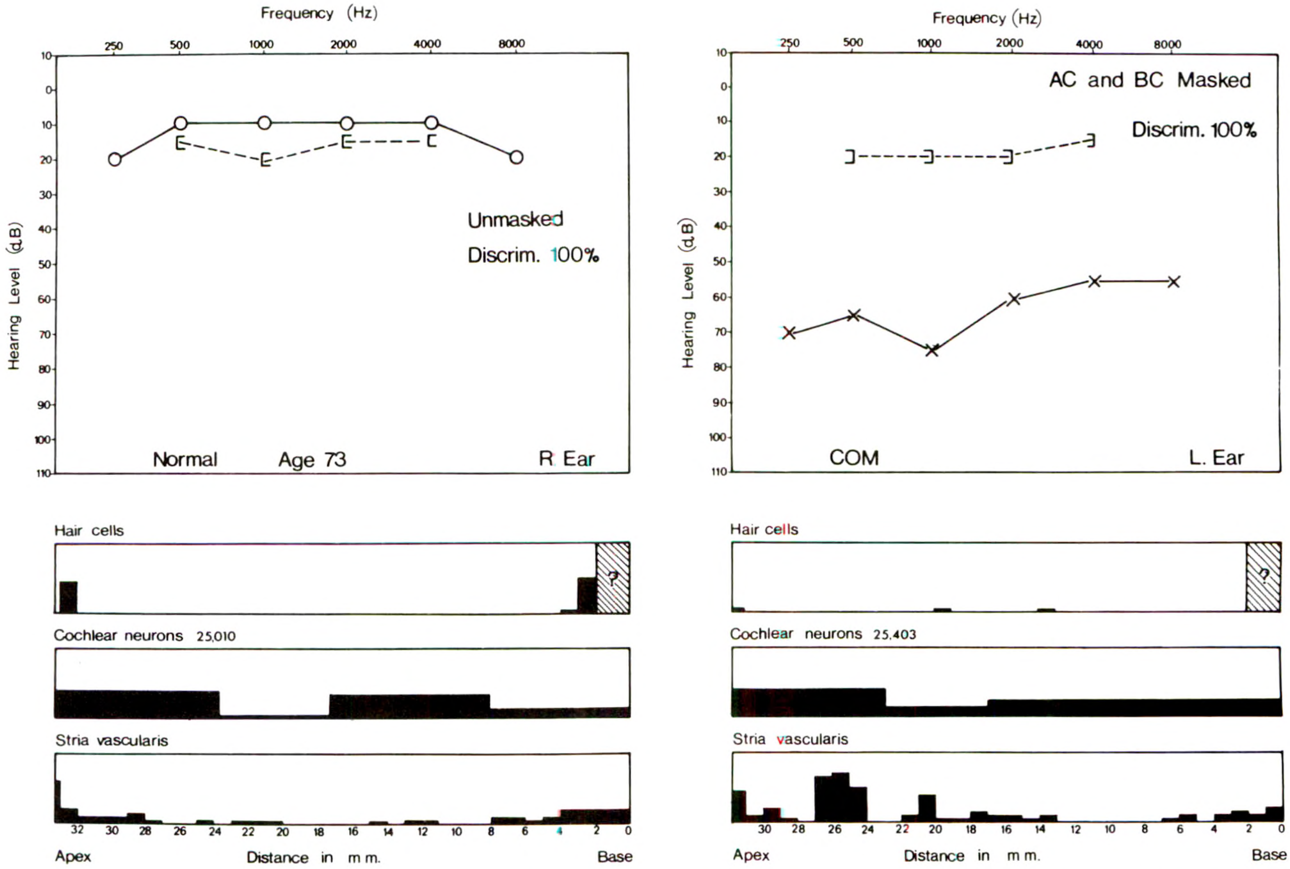


Fig 16. (Case 12) This patient at age 69 complained of an intermittent discharge from the left ear dating from childhood. Examination revealed a perforation of the pars tensa in the left ear with a mucoid discharge. She died of carcinoma of the breast with a terminal bronchopneumonia at age 75. There was no histopathology in the right middle ear. In the left ear the pars tensa was missing with epidermization of the middle ear sealing off the protympanum. The manubrium of the malleus was embedded in fibrous tissue; the long process of incus and stapes superstructure were absent. There was fibrocystic and osseous sclerosis of the peripheral mastoid.

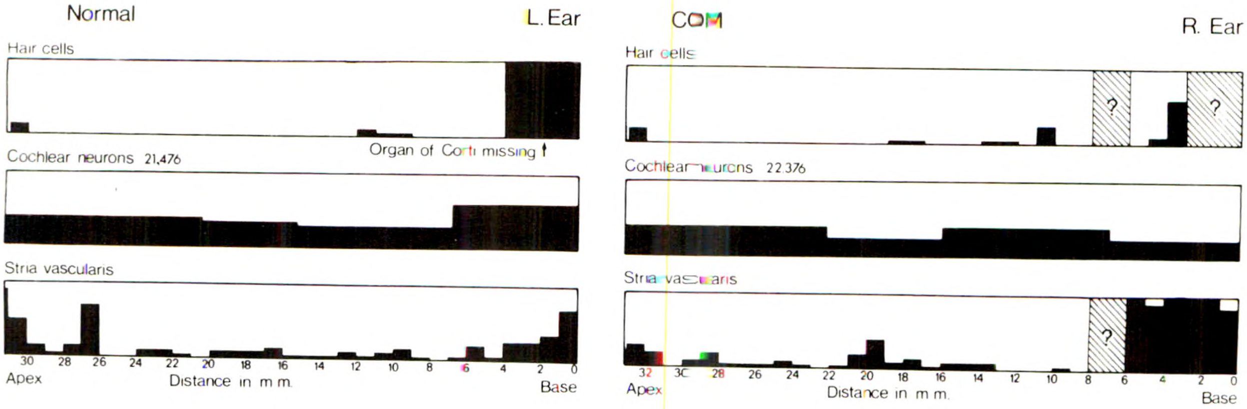


Fig 17. (Case 13) This patient had had bilateral ear ache and otorrhea in childhood. At age 51 following swimming, she developed discharge from the right ear. The left tympanic membrane was retracted, and the right had a posteroinferior perforation. No audiometry was performed. Treatment was given for bilateral otitis externa at age 53, and she died at age 74 of a cerebral hemorrhage. The minimal histopathology in the left middle ear was hyalinization in an inferior replacement tympanic membrane, with adhesion to the long process of incus. The organ of Corti was completely missing in the basal 4 mm. The right ear had tympanosclerosis in the tympanic membrane with a posteroinferior perforation and surrounding keratin debris. In the sections available no hair cells or stria vascularis were represented from the seventh and eighth millimeters. This patient probably had an acute otitis media in the left "normal" ear in childhood.

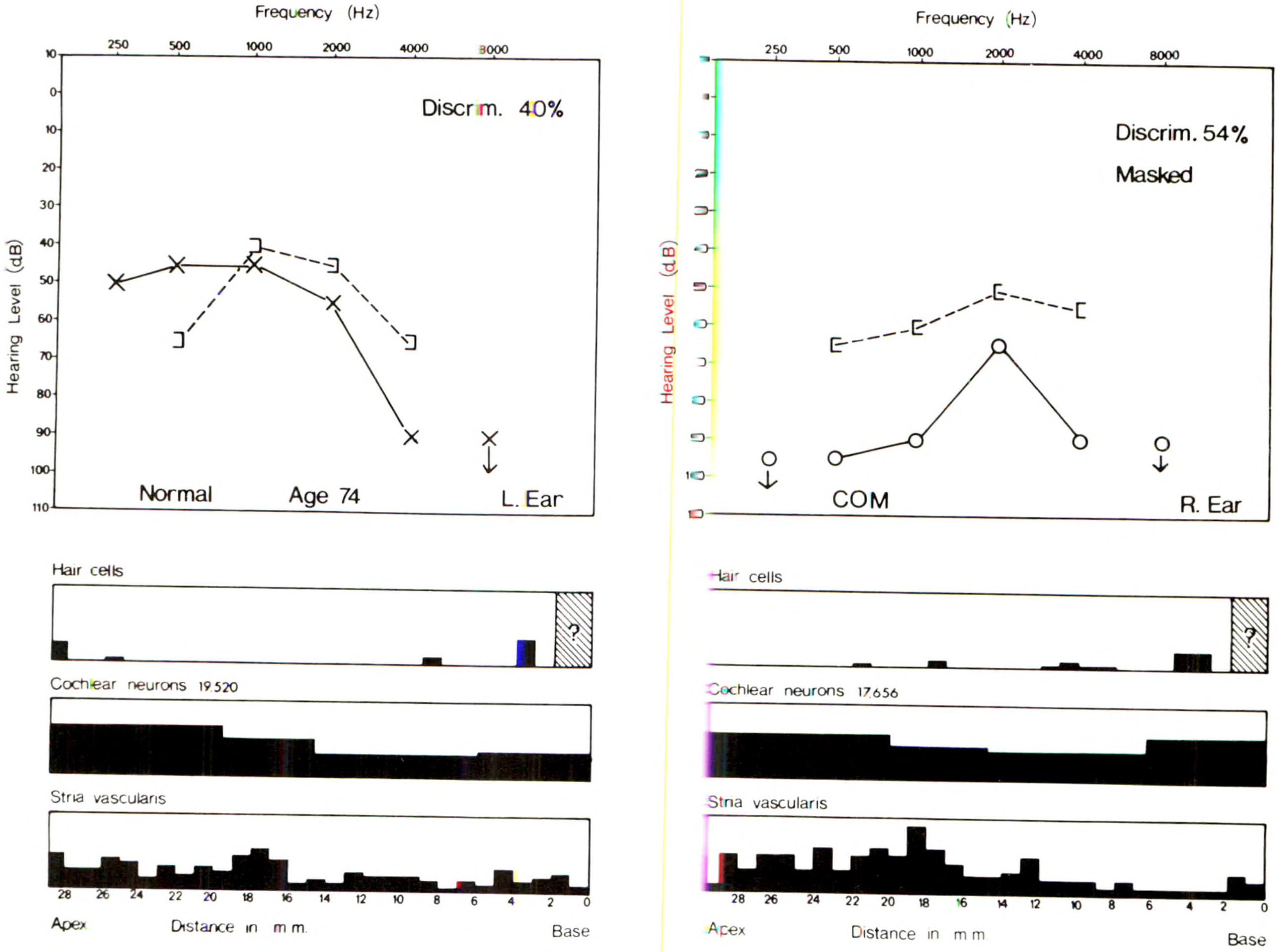


Fig 18. (Case 14) This patient had had an ear infection in childhood. He complained of progressive hearing loss in his last years of life, and at age 74 was noted to have a thickened left tympanic membrane and a dry subtotal perforation of the right. He died at age 79 of a myocardial infarction. The minimal histopathology in the left ear was thickening of the tympanic membrane and middle ear mucosa, and a replacement membrane inferiorly. The right tympanic membrane had a large inferior perforation with the remainder greatly thickened with hyalinization anteriorly. The manubrium of the malleus and the incus were partially eroded. There was thickening of the middle ear mucosa and almost total fibro-osseous obliteration of the mastoid. This patient probably had an acute otitis media in the left "normal" ear in childhood.

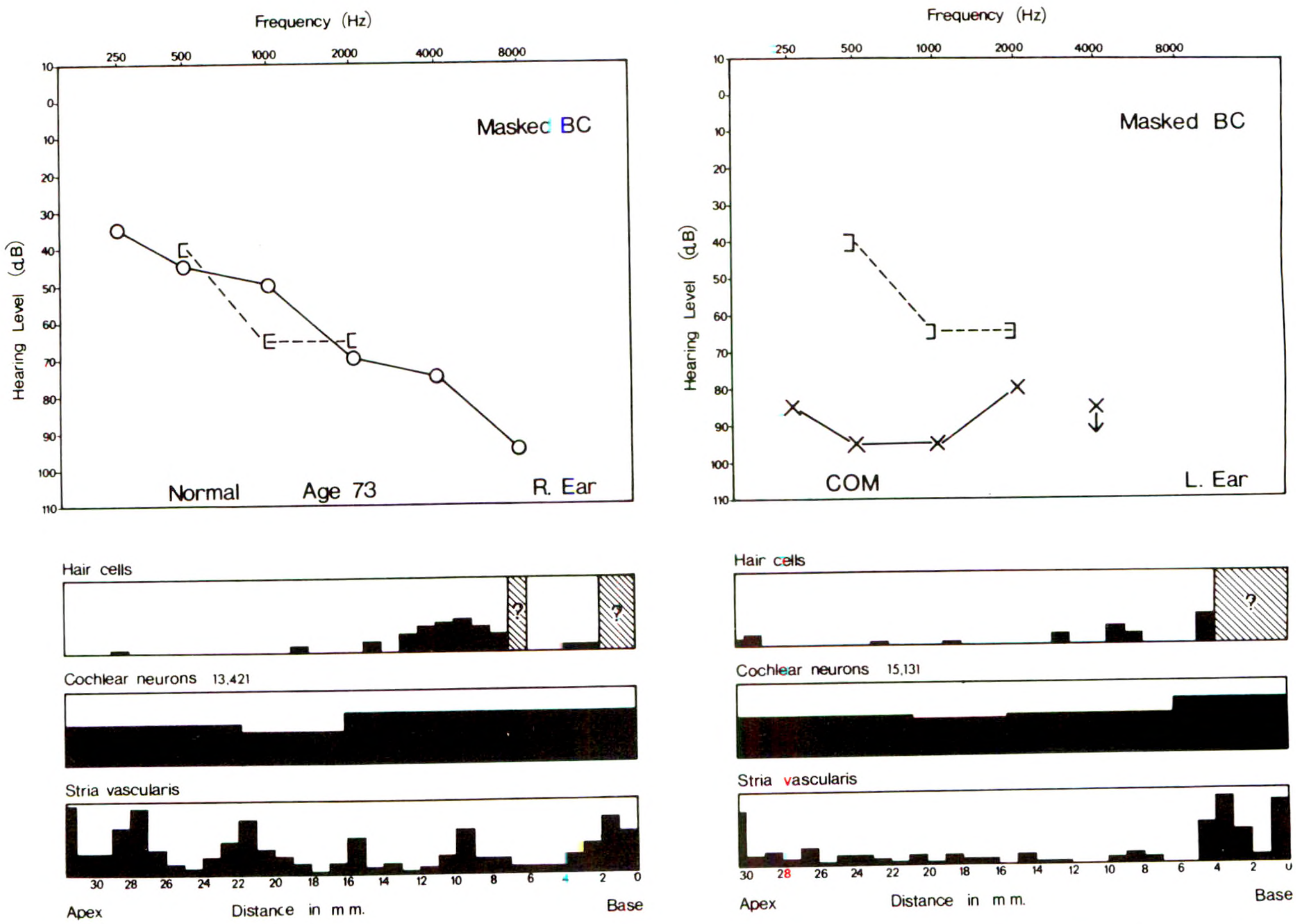


Fig 19. (Case 15) This patient complained only of hearing loss at age 73. Examination revealed a retracted left tympanic membrane. He died at age 83 of a myocardial infarction. The minimal histopathology of the right middle ear was retraction of the tympanic membrane onto the long process of incus and fibrous thickening of the submucosa of the middle ear. There was also otosclerosis anterior to the oval window and in the stapes footplate but without fixation. The cochlear endosteum was involved in areas corresponding to millimeters 19 to 21, and 28 and 29 of the organ of Corti. In the serial sections available no hair cells were represented from the seventh millimeter. The left tympanic membrane was intact with tympanosclerosis present anteriorly. There was a posterosuperior retraction pocket with erosion of the scutum and epidermization of the incus. The manubrium of the malleus, long process of incus, and stapes superstructure were eroded. There was fibrosis in the mastoid. The patient may have had an acute otitis media in the right "normal" ear in the past.

evidence of inflammation spreading across the round window to the scala tympani. In the 12 pairs of bones, no precipitates as generalized as those shown by Paparella et al[9] were found. A fine line of eosinophilic precipitate was frequently seen lining the scala tympani or vestibuli, but this was almost as common in the normal ears (Table 6). It is probable that this precipitate was diffusely spread throughout the scala but settled out during preparation. Its finding in the normal ear as well suggests that infection was not the cause. In one of the three cases described separately (case 14), the precipitates were more extensive and more deeply stained throughout than in the opposite normal ear, or in any of the other 28 ears, and this was the only case in which the precipitate convincingly appeared to be due to the infection. The difficulty in interpretation of perilymph precipitates has previously been referred to by Dean and Wolff.[29] The few round mononuclear cells lining the inside of the round window membrane were a consistent finding in both normal and infected ears, and were presumed to be endothelial cells desquamated from the membrane.

The range of types of infection in these temporal bones encompasses the common pathology found in COM, and although in some ears the duration of infection was not known, in others it was known to be of considerable duration. It would seem likely that if COM were going to cause hair cell destruction, some evidence should have been found in this study. It has not been, and suggests that the labyrinth provides a barrier which is effective in preventing destruction of neurosensory elements in the cochlea, unless a suppurative labyrinthitis supervenes. Such an eventuality does cause this destruction by invasion via the oval or round windows, fistulae, lymphatics, or vascular channels, but it is now a relatively rare event, mainly because of the effectiveness of antibiotics. The cause of breakdown in the labyrinthine barrier is not clearly known.

In summary, COM causes an increased threshold of hearing, as measured by bone conduction, which may be due to the alteration of middle or inner ear mechanics. It could also be due to the infection (or its treatment by topical ototoxic drugs) causing damage to sensorineural structures which is not visible on light microscopy. The finding that hair cells and nerve cells are not destroyed by an uncomplicated chronic suppurative otitis media indicates that the abnormally high bone conduction thresholds frequently seen in this condition may well be due to changes in the mechanics of sound transmission, and such explanations should be more seriously entertained.

ACKNOWLEDGMENTS — The authors gratefully acknowledge the assistance of Diane Jones for the preparation of histological materials, Laurel Cook for the artwork, Carla Wittig and Alan Lucas for the photography, and Carol Oda for assistance in preparing the manuscript.

REFERENCES

1. Paparella MM, Sugiura S. The pathology of suppurative labyrinthitis. Ann Otol Rhinol Laryngol 1967; 76:554-86.

2. Hůlka JH. Bone conduction changes in acute otitis media. Arch Otolaryngol 1941; 33:333-50.

3. Lierle DM, Reger SN. Correlations between bone and air conduction acuity measurements over wide frequency ranges in different types of hearing impairments. Laryngoscope 1946; 56: 187-224.

4. Carhart R. Effect of stapes fixation on bone conduction response. In: Schuknecht HF, ed. Otosclerosis. Boston: Little, Brown and Co, 1962:175-97.

5. Gardenghi G. Contributo allo studio della funzione cocleare nell'otite media purulenta cronica. Boll Malattie Orecchio Gola Naso (Firenze) 1955; 73:587-606.

6. Bluvshtein GM. The audiological characteristics of chronic suppurative otitis media. Vest Otorinolaringol 1963; 25:64-72.

7. Schuknecht HF. The effect of aging on the cochlea. In: Graham AB, ed. Sensorineural hearing processes and disorders. Boston: Little, Brown and Co, 1967:393-401.

8. Paparella MM, Brady DR, Hoel R. Sensori-neural hearing loss in chronic otitis media and mastoiditis. Trans Am Acad Ophthalmol Otolaryngol 1970; 74:108-15.

9. Paparella MM, Oda M, Hiraide F, Brady D. Pathology of sensorineural hearing loss in otitis media. Ann Otol Rhinol Laryngol 1972; 81:632-47.

10. English GM, Northern JL, Fria TJ. Chronic otitis media as a cause of sensorineural hearing loss. Arch Otolaryngol 1973; 98:18-22.

11. Meyerhoff WL, Kim CS, Paparella MM. Pathology of chronic otitis media. Ann Otol Rhinol Laryngol 1978; 87:749-60.

12. Shambaugh GE Jr. Complications of otitis media. In: Wiet RJ, Coulthard SW, eds. Proceedings of the second national conference on otitis media. Columbus, Ohio: Ross Laboratories, 1979:48-50.

13. Beales PH. Chronic suppurative otitis media — assessment. In: Ballantyne J, Groves J, eds. Scott-Brown's diseases of the ear, nose and throat. 4th ed. London: Butterworth and Co, Ltd, 1979:256.

14. Paparella MM, Goycoolea MV, Meyerhoff WL, Shea D. Endolymphatic hydrops and otitis media. Laryngoscope 1979; 89:43-54.

15. Stewart TJ, Belal A. Surgical anatomy and pathology of the round window. Clin Otolaryngol 1981; 6:45-62.

16. Senturia BH, Bluestone CD, Klein JO, Lim DJ, Paradise JL. Report of the ad hoc committee on definition and classification of otitis media and otitis media with effusion. Ann Otol Rhinol Laryngol 1980; 89 Suppl 68:3-4.

17. Schuknecht HF. Cochlear otosclerosis. A continuing fantasy. Arch Otorhinolaryngol 1979; 222:79-84.

18. Schuknecht HF. Temporal bone removal at autopsy. Arch Otolaryngol 1968; 87:129-37.

19. Guild SR. A graphic reconstruction method for the study of the organ of Corti. Anat Rec 1921; 22:141-57.

20. Schuknecht HF. Techniques for study of cochlear function and pathology in experimental animals. Arch Otolaryngol 1953; 58:377-97.

21. Otte GJ. Estudio del ganglio espiral y su relacion con la discriminacion. Rev Otorhinolaringol 1968; 28:89-99.

22. Ota CY, Kimura RS. Ultrastructural study of the human spiral ganglion. Acta Otolaryngol (Stockh) 1980; 89:53-62.

23. Konigsmark BW. Methods for the counting of neurons. In: Nauta WJH, Ebbesson SOE, eds. Contemporary research methods in neuroanatomy. Berlin: Springer-Verlag, 1970:315-40.

24. Otte J, Schuknecht HF, Kerr AG. Ganglion cell population in normal and pathological human cochleae. Implications for cochlear implantation. Laryngoscope 1978; 88:1231-46.

25. Yamashita T, Schuknecht HF. Apical endolymphatic hydrops. Arch Otolaryngol 1982; 108:463-6.

26. Schuknecht HF. Pathology of the ear. Cambridge, Mass: Harvard University Press, 1974.

27. Koenig W. A new frequency scale for acoustic measurements. Bell Lab Rec 1949; 27:299-301.

28. Tonndorf J. Bone conduction. In: Tobias JV, ed. Foundations of modern auditory theory. Vol II. New York: Academic Press, 1972:197-237.

29. Dean LW, Wolff D. Pathology and routes of infection in labyrinthitis secondary to middle ear otitis. Ann Otol Rhinol Laryngol 1934; 43:702-17.

ANNALS PUBLISHING COMPANY
4507 LACLEDE AVENUE
ST LOUIS, MISSOURI 63108

COPYRIGHT 1983, ANNALS PUBLISHING COMPANY

Rec.
27.10.83

EFFECTS OF HYPEROSMOLAR SOLUTIONS ON THE LABYRINTHINE FLUID PRESSURES

I. EFFECTS OF GLYCEROL AND UREA TESTS

II. EFFECTS OF MANNITOL TESTS

BJÖRN I. R. CARLBORG, MD, PHD
JOSEPH C. FARMER, JR, MD

UNIVERSITY [illegible] OF MEDICINE
LIBRARY

Supplement 104 — May-June 1983, Volume 92, Number 3, Part 2
ANNALS OF OTOLOGY, RHINOLOGY & LARYNGOLOGY
ANNALS OF HEAD & NECK MEDICINE & SURGERY

The one physicians lean on...

N 0071-2220-17
ELIXIR
Benadryl®
(Diphenhydramine Hydrochloride Elixir)
Caution–Federal law prohibits dispensing without prescription.
4 FLUIDOUNCES
PARKE-DAVIS

PARKE-DAVIS
Div of Warner-Lambert Co
Morris Plains, NJ 07950 USA

) 1981 Warner-Lambert Company
[illegible]

EFFECTS OF HYPEROSMOLAR SOLUTIONS ON THE LABYRINTHINE FLUID PRESSURES

I. EFFECTS OF GLYCEROL AND UREA TESTS

II. EFFECTS OF MANNITOL TESTS

Björn I. R. Carlborg, MD, PhD
Joseph C. Farmer, Jr, MD

EFFECTS OF HYPEROSMOLAR SOLUTIONS ON THE LABYRINTHINE FLUID PRESSURES

I. EFFECTS OF GLYCEROL AND UREA TESTS

BJÖRN I. R. CARLBORG, MD, PHD
MALMÖ, SWEDEN

JOSEPH C. FARMER, JR, MD
DURHAM, NORTH CAROLINA

An investigation was performed on the efficiency of glycerol and urea in reducing the inner ear fluid pressure and to determine whether such a pressure reduction mainly is related to a direct osmotic effect upon the labyrinth or to a decrease in the cerebrospinal fluid (CSF) pressure via the cochlear aqueduct (CA). Glycerol and urea were infused intravenously into cats with the CA patent and with the CA instrumentally blocked. Continuous measurements of the perilymphatic, CSF, central venous and arterial pressures were performed. During the infusion of the drugs when the CA was patent, a transient increase in perilymphatic pressure was seen with glycerol but not with urea. The perilymphatic pressure closely followed changes in CSF pressure induced by glycerol and urea, and the main long-standing effect was an equal reduction of the CSF and perilymphatic pressure. However, instrumental blockage of the CA significantly reduced the influence of the CSF pressure and increased the influence of the arterial pressure upon the perilymphatic pressure. Still, after drug infusion, the perilymphatic and CSF pressures were reduced parallel to each other. There was no significant difference between the effects of glycerol and urea postinfusion. The results indicate that the inner ear pressure reductions induced by glycerol and urea mainly are related to direct osmotic effects on the labyrinth. The patency of the CA does not significantly influence the main long-standing effects, but does influence the early transient effects of the drugs on perilymphatic pressure.

INTRODUCTION

On the basis of clinical studies of Menière's disease numerous authors advocate that a positive glycerol test, ie, improvement of hearing after oral administration of glycerol, is specific for an endolymphatic hydrops.[1-3] Glycerol and urea have a well-documented osmotic effect by which the cerebrospinal fluid (CSF) pressure is reduced.[4,5] This finding, together with the close relationship between the CSF and inner ear fluid pressure, suggests that the positive test results in Menière's disease are caused by a reduction of the perilymphatic and endolymphatic pressure and volume.[1,6] Such a reduction could be induced by a direct osmotic effect on the labyrinth or could be secondary to a decrease in CSF pressure mediated via a patent cochlear aqueduct (CA). Direct and indirect measurements of endolymphatic pressure have indicated that the endolymphatic sac and duct does not efficiently transmit changes in CSF pressure.[7,8]

Clinical[9] as well as histological studies[10] indicate that the CA is variably patent in humans. This finding, plus a 50% to 60% rate of positive urea and glycerol tests in patients with suspected Menière's disease,[11] as well as some reports of a decrease in hearing during these tests,[12,13] would indicate that further investigation of the influence of the CA patency upon these test results is needed. The experimental studies of Juhn and Rybak[14] on the blood-labyrinth barrier have indicated that hyperosmolar solutions may have an osmotic effect on the inner ear. However, these studies as well as a study by Angelborg and Ågerup[15] demonstrating that glycerol induced a reduction of perilymphatic pressure were performed on animals with the CA patent. Consequently the contribution of the CA in these studies, allowing a possible exchange of solutes with the CSF as well as a rapid pressure equilibration,[16] may partially obscure an interpretation of the mechanisms by which hyperosmolar solutions affect the labyrinthine fluid pressure.

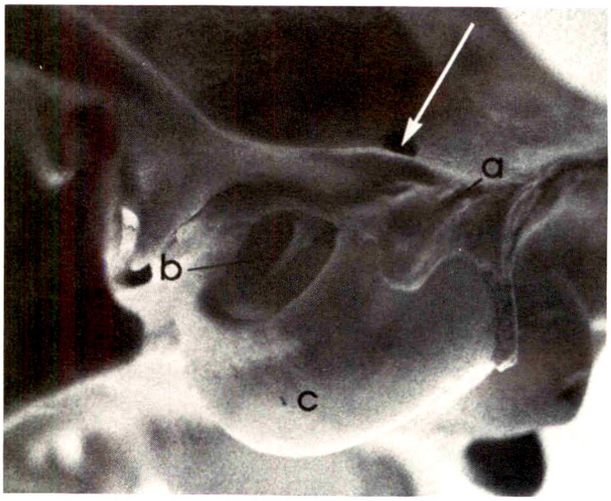


Fig 1. Temporal bone showing extra-aural approach to inner ear. Canal is drilled in frontomediocaudal direction (arrow) cranially to mastoid process (a). b - Malleus; c - Tympanic bulla.

From the Division of Otolaryngology, Department of Surgery, Duke University Medical Center, Durham, North Carolina. This investigation was supported by grants from Fogarty International Center of the National Institutes of Health-International Research Fellowship No. 1 F05 TW03050-01 IARG, the National Institutes of Health grant No. HL07896. and Tysta Skolan, Sweden.

Dr. Carlborg was an NIH-Fogarty Research Fellow from October 1981 until April 1983.

CORRESPONDENCE — Björn Carlborg, MD, PhD, Department of Otolaryngology, Malmö General Hospital, S-21401, Malmö, Sweden.

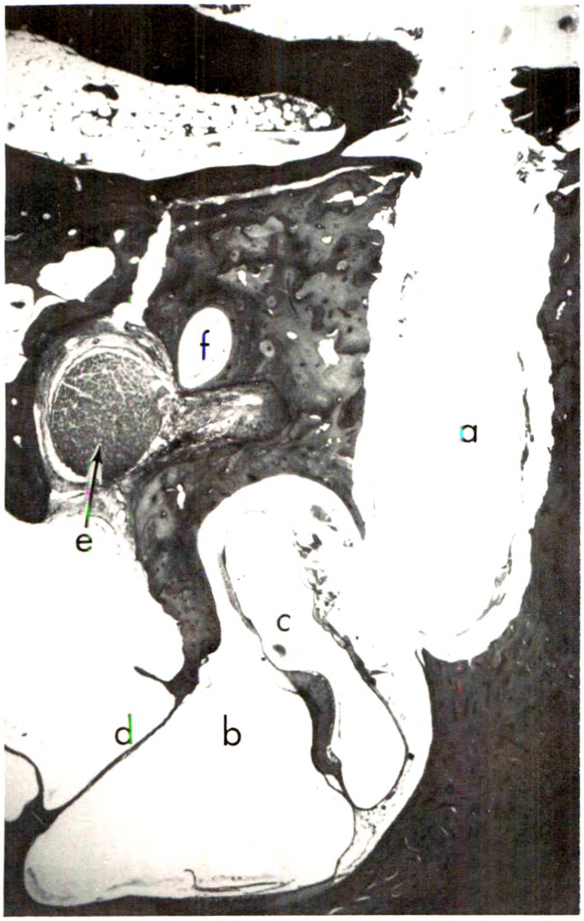


Fig 2. Histology section of temporal bone. Canal (a) drilled via the extra-aural approach into vestibule (b). No bleeding was seen in inner ear. c - Utricle; d - Stapes; e - Facial nerve; f - Semicircular canal.

The aim of the present study was to investigate the effects of urea and glycerol on the perilymphatic pressure before and after obstruction of the CA in the cat. The study was initiated by the following questions:

1. Will glycerol and urea reduce the perilymphatic pressure, and, if so, will they be equally effective?
2. Will a pressure reduction be induced by a direct osmotic effect on the labyrinth or merely be secondary to a change in CSF pressure?
3. Will glycerol and urea induce a transient increase in the inner ear fluid pressure?

METHODS AND MATERIALS

Twenty-two cats weighing 2.5 to 3.5 kg were used. Pentobarbital was used for intravenous (IV) anesthesia with an induction dose of 25 mg/kg. A tracheostomy was performed and ventilation was maintained with a respirator. Arterial blood gas levels were monitored regularly and maintained at physiologic levels.

The perilymphatic pressure (PPL) was measured in the vestibule via a canal drilled with an extra-aural approach through the temporal bone, thereby leaving the ear canal and middle ear intact

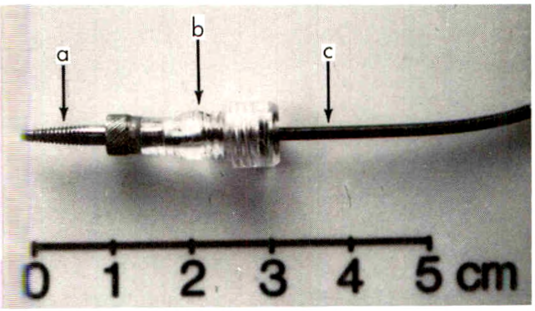


Fig 3. "Inner ear cannula": threaded metallic cannula (a) with rigid plastic adaptor (b) mounted on top of it. Microtip pressure transducer (c) is inserted through a rubber "O" ring into the adaptor. (Reprinted with permission.[18])

(Figs 1 and 2). The drilled canal was filled with artificial CSF.[17] A metallic cannula with a microtip pressure tranducer mounted on top (Fig 3) was screwed into the canal and sealed. The total fluid volume of the cannula-transducer assembly was 6 mm^3.[18]

The cerebrospinal fluid pressure (PCSF) was measured in the lateral ventricle via a metallic cannula with a microtip transducer mounted on top.

The central venous (PCV) and arterial pressure (PA) were recorded from microtip pressure transducers connected to cannulae placed into the external jugular vein and the femoral artery.

The PPL, PCSF, PCV and PA were measured continuously. Microtip pressure transducers PC 350 5F (Millar Instruments Inc, Houston) were used with a volume displacement of 1×10^{-3} mm^3/100 mm Hg and a sensitivity of 1.2-5 mV/V/100 mm Hg. The transducers were calibrated before and after each experiment. The integrated mean pressure levels were calculated from the recordings of a Gould Brush 200 ink recorder.

The CA was blocked via the tympanic bulla in 14 animals. The CA was exposed with a diamond drill posteromedial to the round window. The aqueduct was completely transected over a distance of 0.2 to 0.5 mm and occluded with amalgam. In eight animals the inferior cochlear vein was also exposed and obstructed. Before and after blocking of the CA, functional tests of the patency of the CA[9] were performed by infusion of artificial CSF into the subarachnoid space.

The main experiments consisted of IV infusion of equiosmolar doses of 50% glycerol or 30% urea, ie, 1.2 g/kg and 0.8 g/kg, respectively. The dose selected was equiosmolar per body weight to that given orally in humans undergoing glycerol tests for Meniere's disease. The infusion rate, controlled with an infusion pump, was varied among animals from 1.2 ml/min to 5 ml/min. Urea was given to five animals before and to six others after blocking the CA. Five animals received glycerol before obstruction of the CA and two of these also received glycerol four hours after blocking the CA. Six animals were treated with glycerol only after the aqueduct was obstructed.

Arterial blood samples for serum osmolality, serum urea, and plasma glycerol concentrations were drawn prior to infusion, and 5 to 1[illegible], 30, and 60 minutes after the end of the infusion.

Statistical calculations were as follows: All results were expressed in mean values ± standard error of the mean (SEM). Student's t test was used for paired and unpaired observations. $P < 0.05$ was considered statistically significant.

RESULTS

INTRACRANIAL INFUSION

Comparison of Patent and Blocked CA. The hydrodynamic relationship between the CSF and the perilymph was tested in all animals by intracranial

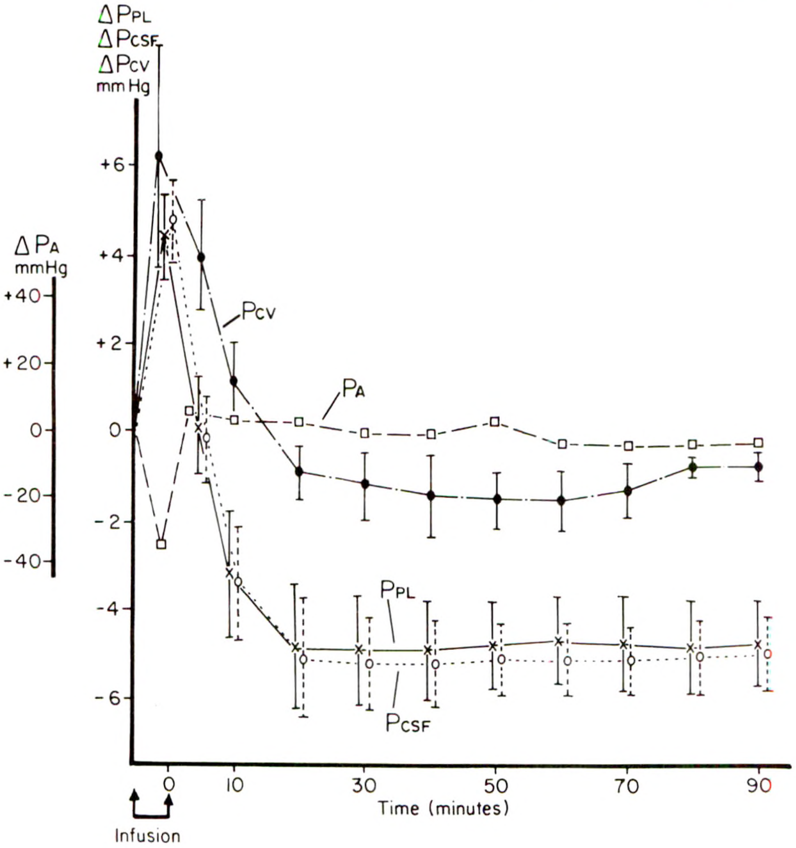


Fig 4. Glycerol infusion (arrows) in five animals with cochlear aqueduct patent. Mean change in pressure ± SEM is given for perilymphatic (△ PPL———), CSF (△PCSF---), central venous (△PCV —·—·—·) and arterial pressure (△PA———). Scale for △PA is to left of scale for △PPL, △PCSF, and △PCV.

infusion (0.2 ml/min) of artificial CSF 1½ to two hours before and after glycerol or urea administration. When the CA was patent, intracranial infusion induced a change in PPL that was always similar to that of the PCSF and with a time lag not exceeding 5 seconds. No significant pressure difference was found between the PCSF and PPL either before or after infusion. Upon blockage of the CA or the CA plus the inferior cochlear vein, the PPL immediately fell and within minutes returned to the level before transection. No significant difference was found between the PPL and PCSF when experimental conditions were kept stable after the blockage. However, intracranial infusion revealed a considerable time lag in the PPL response to changes in CSF pressure. Generally ten to 20 mintues elapsed before the PP regained the same level as the PCSF.

GLYCEROL EFFECTS

CA Patent (Fig 4). The mean PPL and PCSF levels prior to the experiments were 7.5 ± 1.9 mm Hg and 7.6 ± 2.3 mm Hg, respectively. Substantial, transient pressure changes occurred during and immediately after the infusion of glycerol. Control experiments with similar volumes of saline did not have this effect. During glycerol infusion (5 ml/min in five animals) the PA fell (34 ± 10 mm Hg) and the PCV rose (6.2 ± 2.3 mm Hg) in all animals. This increase in PCV was accompanied by a concomitant rise in the PCSF (4.8 ± 0.9 mm Hg) similar to that of the PPL (4.6 ± 0.9 mm Hg). After the end of the infusion the PCV immediately and gradually started to fall and was accompanied by a greater and faster decline in the PCSF and the PPL. The long-standing effect of glycerol infusion was an equal reduction of CSF and perilymph pressures. The PPL closely followed any change in PCSF and there was no significant difference between the pressures either during or after the infusion. The maximum reduction of PPL (5.0 ± 1.2 mm Hg) and PCSF (5.2 ± 1.1 mm Hg) was reached in about 30 minutes and persisted for the duration of the experiment, 90 minutes.

CA Blocked (Fig 5). The mean PPL and PCSF preceding the experiments were 10.4 ± 1.2 mm Hg and 10.4 ± 1.7 mm Hg, respectively. The infusion rate was now reduced to 1.2 ml/min to reveal its influence of the dynamic changes of pressure during the infusion. The fall in PA (19 ± 10 mm Hg) and concomitant rise in PCV (3.4 ± 1 mm Hg) were diminished compared to fast infusion experiments, and so was the subsequent rise in PCSF. During the infusion, the PPL did not follow abrupt increases in PCSF or PCV but declined simultaneously with the PA. At the end of the infusion, a significant difference ($p < 0.001$) was found between the PPL and PCSF. After the infusion, there was a similar reduction of the CSF and perilymph pressure, both reaching a maximum reduction (about 7.9 ± 0.8 mm Hg) in 30 to 50 minutes that persisted for the duration of the experiment, 90 minutes.

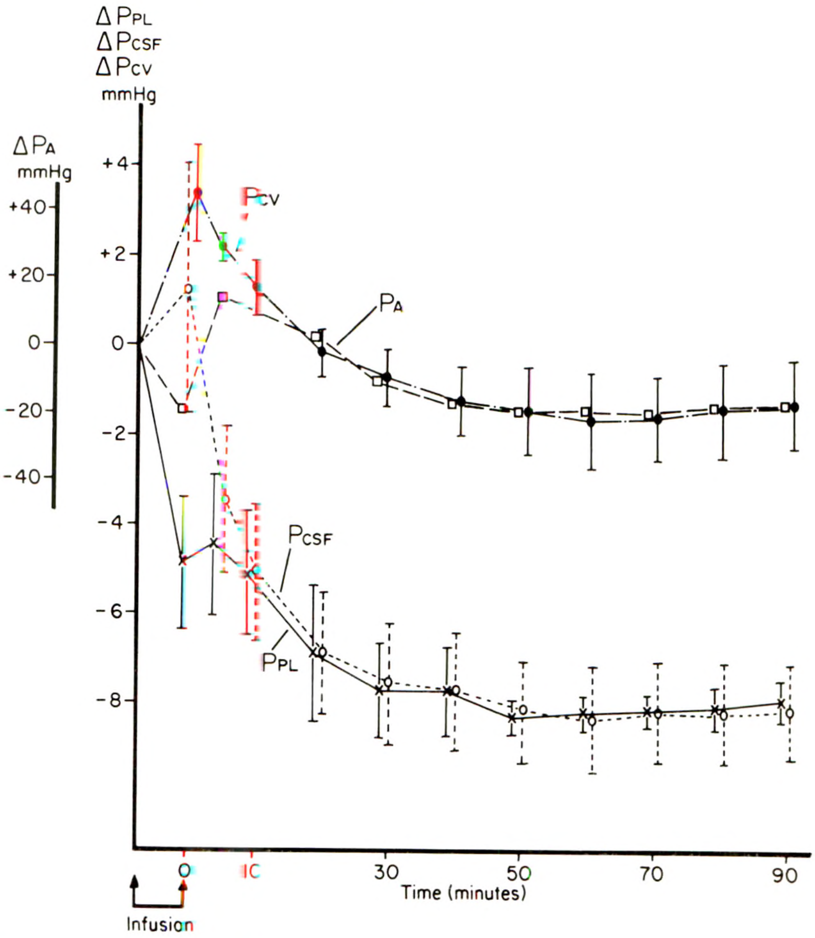


Fig 5. Glycerol infusion (arrows) in six animals with cochlear aqueduct obstructed. See Fig 4 for symbols and scale.

Comparison of Patent and Blocked CA. A significantly different effect was seen during the infusion of glycerol on the PPL of animals with the CA blocked compared to those with the CA patent. When the CA was occluded, the PPL did not follow abrupt changes in PCSF or PCV but changed concomitantly and in the same direction as the PA.

After the end of the infusion when the PA and PCV stabilized toward the preinfusion levels, the PPL quickly reached the same level of pressure reduction as the PCSF despite the closed CA. The main late effect of glycerol on the PPL and the PCSF was the same regardless of the patency of the CA.

Experiments with a low infusion rate (Fig 5) showed a tendency toward a slightly greater reduction of both the PCSF and PPL than experiments with a rapid infusion rate (Fig 4). This difference was statistically significant ($p<0.05$) only between 50 to 80 minutes postinfusion, and may also be seen in light of the slightly higher preinfusion levels of the PCSF and PPL in the low-rate infusion experiments.

Two animals receiving glycerol before occlusion of the CA were also given glycerol four hours later when the aqueduct had been obstructed. The PPL and PCSF, still reduced from the first experiment, were decreased but to a lesser extent by the second infusion.

UREA EFFECTS

CA Patent (Fig 6). The mean PPL and PCSF preceding the urea infusion were 8.1±1.8 mm Hg and 3.2±1.8 mm Hg, respectively. The PA was reduced in four of five animals during the infusion. Concomitantly a small increase in PCV (1.8±0.9 mm Hg) was seen, whereas the PCSF and PPL were reduced. At the end of the infusion, the PA and PCV gradually stabilized close to the preinfusion levels whereas the PCSF and the PPL continued to decline. At no time during the experiment was there any significant difference between the PCSF and PPL. The maximum pressure reduction of about 6.6±1.0 mm Hg was reached in 40 to 50 minutes postinfusion and persisted during the experiment.

CA Blocked (Fig 7). Prior to the infusion of urea the mean PPL of the six animals was 12.5±1.3 mm Hg and the mean PCSF was 11.8±1.5 mm Hg. During the infusion there was an increase in PCV (1.0±0.2 mm Hg) while the PA, PCSF and PPL fell. However, the reduction of the PPL during the infusion was significantly greater than that of the PCSF ($p<0.05$). The increase in PA postinfusion coincided with a transient rise in PPL, whereas the PCSF was not seen to be affected by this. After the end of the infusion there was no significant difference between the PPL and PCSF. Both pressures reached a maximum reduction of about 6.1±1.4 mm Hg and

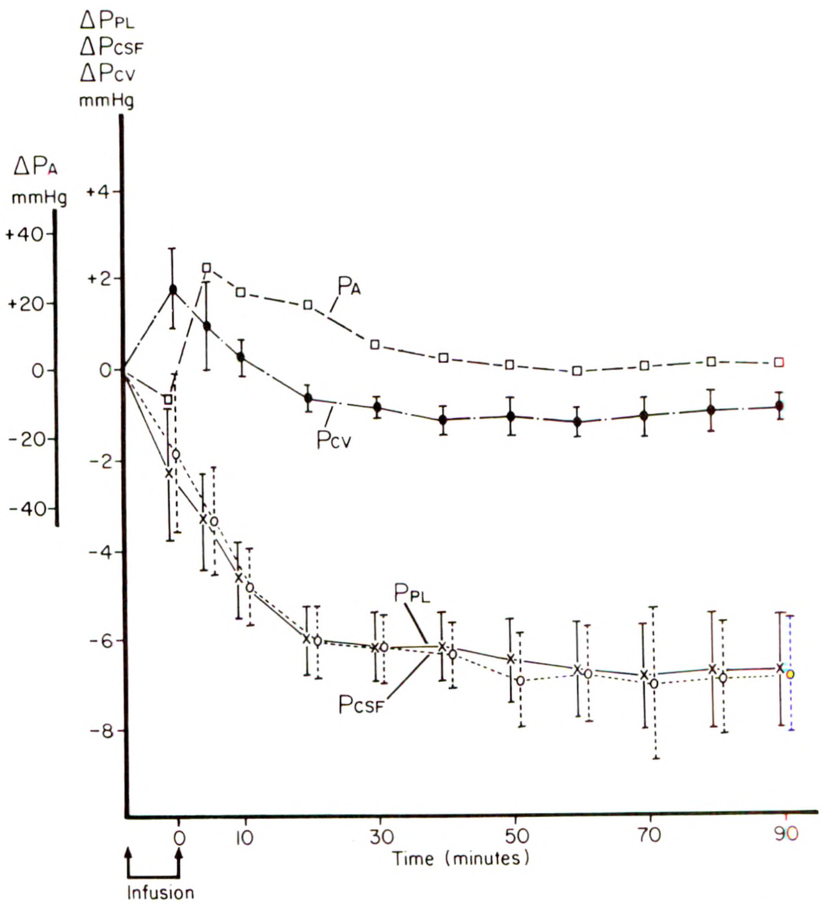


Fig 6. Urea infusion (arrows) in five animals with cochlear aqueduct patent. See Fig 4 for symbols and scale.

6.9 ± 0.75 mm Hg, respectively, in about 50 minutes.

Comparison of Patent and Blocked CA. During urea infusions with the CA blocked, as during glycerol infusions, changes in the PPL did not closely follow alterations in the PCSF but tended to follow changes in PA. When the CA was patent the PPL followed any variations in the PCSF. The early effects of urea included a decrease in PA as well as PCSF, and the early decline in PPL was seen regardless of the patency of the CA. However, the decline in PPL was significantly greater when the CA was blocked ($p<0.05$). The late reduction of the PPL and PCSF was similar with the CA patent and blocked.

COMPARISON OF GLYCEROL AND UREA EFFECTS

The late long-standing effect after the infusion of glycerol and urea was a reduction of CSF and perilymphatic pressure. There were no significant differences in the maximum pressure reductions caused by glycerol or urea on the PPL or PCSF regardless of the patency of the CA. These pressures remained reduced for the duration of the experiment, 90 minutes. The early effects, during the infusion of glycerol and urea always included a transient increase in PCV and a decrease in PA. The PCV rise was accompanied by a transient increase of the mean PCSF in animals given glycerol. However, the rise in the PCV (1.4 ± 0.5 mm Hg in 11 cats) during urea infusion was significantly lower ($p<0.05$) than from glycerol (4.8 ± 1.2 mm Hg) and was not accompanied by a PCSF increase. On the contrary, the PCSF fell during the urea infusion. Since the PPL followed any change in PCSF when the CA was patent, the PPL was transiently increased by glycerol and decreased by urea infusion. Blockage of the CA did not significantly affect the reactions of the CSF and CV pressure after glycerol or urea infusions but apparently reduced the influence of the PCSF and increased the influence of the PA on the PPL. With the CA obstructed the perilymph pressure was seen to fall rapidly during the infusion of glycerol and urea, and the decline of the PPL was significantly greater than that of the PCSF, suggesting an early osmotic dehydration of the inner ear as well as a dependency upon the PA.

Animals in which the inferior cochlear vein was blocked together with the CA did not seem to show any different effects on changes in PPL and PCSF compared to animals with occlusion of only the CA.

BLOOD SAMPLES

Serum osmolality, serum urea, and plasma glycerol levels showed peak values in the first sample (five minutes after the infusion), ie, the time of maximum dynamic pressure effects. Urea and glycerol induced an increase in serum osmolality of 28 ± 3 and 27.8 ± 3 mosm/kg respectively at five minutes, and 19.4 ± 3.4 and 15.6 ± 2.7 mosm/kg

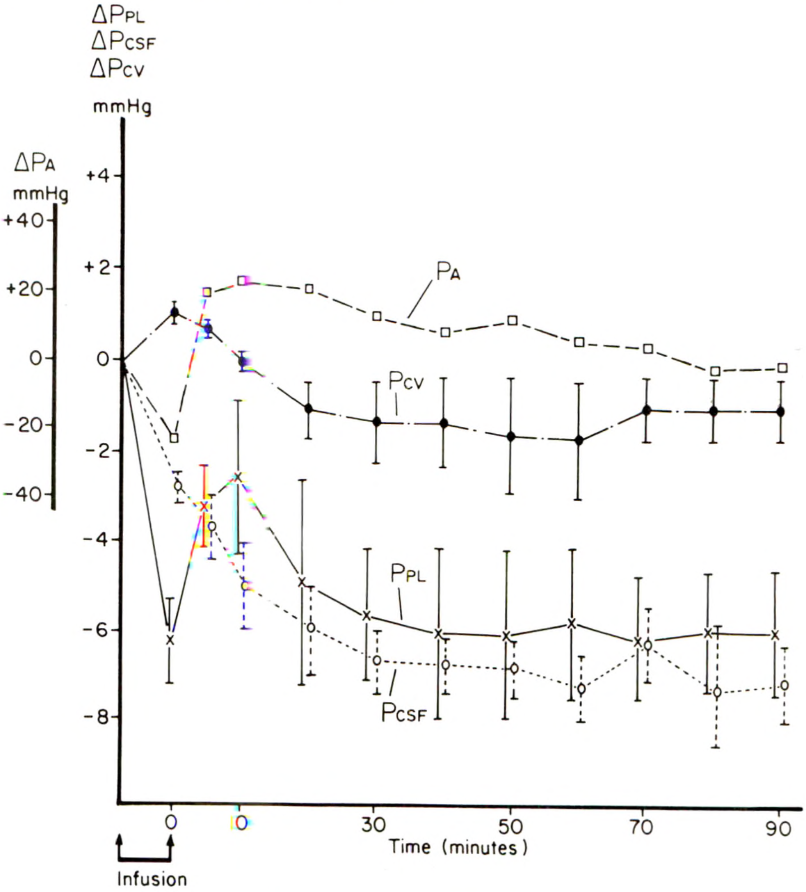


Fig 7. Urea infusion (arrows) in six animals with cochlear aqueduct obstructed. See Fig 4 for symbols and scale.

respectively at 60 minutes after the infusion. Serum urea was increased by 18.8 ± 1.3 and 11.8 ± 0.8 at five and 60 minutes respectively after the infusion.

DISCUSSION

The temporary improvement of hearing noted during the urea and glycerol tests in Menière's disease is generally believed to be due to a direct osmotic reduction of the inner ear fluid volume and pressure presumably occurring in the endolymphatic as well as perilymphatic spaces.[1,6] However, experimental data have so far been limited to one study with glycerol demonstrating a reduction in perilymphatic pressure only in animals with the CA patent.[15] Glycerol lowers the CSF pressure by a reduction of the brain volume due to dehydration of the brain tissue.[4,5] Consequently it could not be excluded that the perilymph pressure reduction from glycerol indirectly reflected a reduction in CSF pressure via a patent CA. Thus, the patency of the CA could significantly influence the results of osmotic tests in humans.

Osmotic effects start within minutes after intravenous injection of osmotic diuretics.[20] Analyses of the early effects of glycerol and urea in this study revealed a decrease in arterial pressure and an increase in central venous pressure. These changes can be attributed to vasodilation[21] and to a rapid increase in vascular volume.

Significant increases in central venous pressure have been shown to increase CSF pressure.[22] The early rise in venous pressure from glycerol in this study was indeed accompanied by an increase in CSF pressure (Figs 4 and 5). This indicates that the rise in central venous pressure was great enough to compensate transiently a reduction of intracranial pressure normally expected from osmotic dehydration of the brain.[20] Early effects of urea did not increase the central venous pressure more than 0.9 to 1.9 mm Hg which did not seem to be enough to obscure an early decline of CSF pressure. After the end of the glycerol and urea infusion the arterial and central venous pressures gradually stabilized towards the preinfusion levels. The CSF pressure gradually declined well below that level presumably due to osmotic dehydration. Early effects on the perilymphatic pressure were dependent upon the solution infused and upon the patency of the CA. With the CA patent, the perilymphatic pressure always closely followed any changes in CSF pressure (Figs 4 and 6), apparently due to a rapid pressure equilibration via the patent CA. This finding is in agreement with previous studies with a patent CA[16,19] and obscures interpretation of direct effects of the drugs on the labyrinth.

When the CA was blocked the perilymphatic pressure did not closely follow the early rapid changes in CSF pressure. This was evident from the effects of glycerol and urea (Figs 5 and 7), as well as from intracranial infusion of CSF when the CA was occluded. However, the perilymphatic pressure did change concomitantly and in the same direction as the arterial pressure (Figs 5 and 7). This was noticed during the infusion as well as immediately after the infusion of glycerol and urea. Such sensitivity to abrupt but even moderate variations in arterial pressure has not previously been reported. However, the concept of similar regulatory mechanisms for the perilymphatic pressure and the CSF pressure, influenced by the autoregulated cerebral blood flow, derives from experimental studies with the CA patent.[8,23] The early decline of the perilymphatic pressure with both drugs when the CA was blocked seems to be caused by a combination of arterial pressure fall, osmotic dehydration of the labyrinth, and, possibly in the case of urea, a CSF pressure reduction.

Analyses of the late effects of glycerol and urea (after the infusions ended) revealed a similar reduction of the CSF and the perilymphatic pressures with and without CA blockage. Since arterial and central venous pressure stabilized close to the preinfusion levels, they are not believed to have influenced the late results. Consequently the late effects of glycerol and urea on the perilymphatic pressure seem to be caused by similar direct osmotic dehydration of the labyrinth sufficient enough to decrease the inner ear fluid pressure. Although such a direct effect was obscured when the CA was patent by the osmotic reduction of the CSF pressure, it became noticeable when the aqueduct was blocked.

In the later phase of the glycerol experiments, a tendency toward a slightly greater reduction of the CSF and perilymphatic pressure was noticed when the CA was blocked compared to patent (Figs 4 and 5). This was significant between 50 to 80 minutes postinfusion. The tendency is believed to be related to the lower infusion rate and the slightly, although not significantly higher, preinfusion levels of the CSF and perilymphatic pressure when the CA was occluded.

Investigations of endolymphatic pressure are faced with considerable technical problems and artifacts. Still, there are strong indications that no significant pressure difference exists between the perilymphatic and endolymphatic compartments in the absence of inner ear disease.[7,15,24] This is also supported by studies demonstrating that the endolymphatic membranes cannot withstand a pressure gradient exceeding 2 to 5 cm of water.[7,25] It also seems probable that an osmotic pressure reduction in the endolymphatic and perilymphatic compartments is equal, due to the similarity of the vascular supply. This is further supported by the work of Angelborg and Ågerup[15] on glycerol effects in guinea pigs with the CA patent. Their results indicated a similar reduction of the endolymphatic and perilymphatic pressure but, according to the authors, should be looked upon with reservation. Thus, it seems justified to assume that measurements of animal perilymphatic pressure in this study and others also reflected similar pressure changes occurring in the endolymph.

In patients with Menière's disease glycerol has been reported to cause a 10% higher rate of positive test results than urea.[11] Therefore, if a positive test is proportionally related to a reduction of the inner ear pressure, one might expect a different effect of the two drugs upon the perilymphatic pressures. This was not seen in this study regardless of the patency of the CA. However, comparisons of human clinical and animal experimental results are always difficult. Moreover, the drugs are administered orally to patients and generally with a lower osmotic load for urea.[11,26] In our study equiosmolar doses were used, and it is conceivable that our doses (equiosmolar per body weight to that of the human glycerol test) were high enough to cause a maximum pressure reduction with both drugs whereas this might not be the case in the urea test in man.[26]

Several authors have reported on a transient decrease in hearing during glycerol tests in Menière's disease.[12,13] An explanation for this effect has not yet been found. The present results showed that glycerol caused a transient increase in CSF and inner ear pressure during the infusion when the CA was patent. A rise in inner ear pressure has been reported by some authors to result in a reduction of hearing.[27,28] However, it should be stressed that any pressure rise in humans during the glycerol test is likely to be less pronounced than in this study since glyerol is administered orally to the human.

ACKNOWLEDGMENTS — The authors are grateful to Professor P. Bennett, Director of F.G. Hall Environmental Laboratory, Duke University Medical Center. The authors are also grateful to Mrs C. Lindqvist and Mr G. Turner for skillful technical assistance and to Mr J. Roby for drawing the graphs.

REFERENCES

1. Klockhoff I, Lindblom U. Endolymphatic hydrops revealed by glycerol test. Acta Otolaryngol (Stockh) 1966; 61: 459-62.

2. Sauer RC, Kaemmerle AW, Arenberg IK. The prognostic value of the glycerol test. Symposium on Meniere's disease. Otolaryngol Clin North Am 1980; 13:693-701.

3. Black OF, Møller M, Wall C, Kitch R. Vestibular and auditory responses to glycerol in Meniere's disease. In: Vosteen KH, ed. Meniere's disease. Stuttgart; New York: Georg Thieme Verlag, 1981:151-8.

4. Pappius HM, Loyd A, Dayes LA. Hypertonic urea. Arch Neurol 1965; 13:395-402.

5. Meyer JS, Charney JZ, Rivera VM, Matthew NT. Treatment with glycerol of cerebral oedema due to acute cerebral infarction. Lancet 1971; 2:993-7.

6. Angelborg C, Klockhoff I, Stahle J. Urea and hearing in patients with Meniere's disease. Scand Audiol 1977; 6:143-6.

7. Beentjes BIJ. On the pressure of the endolymphatic, the perilymphatic and the cerebrospinal fluid, with data on the endolymphatic membranes. [Thesis]. Amsterdam: North-Holland Publishing Co, 1970. 68 p.

8. Carlborg B. Pressure regulating mechanisms of the inner ear in the cat. [Thesis]. Malmö, Sweden: Malmö General Hospital, 1980. 144 p.

9. House WF. Meniere's disease: management and theory. Symposium on fluctuant hearing loss. Otolaryngol Clin North Am 1975; 8:515-35.

10. Rask-Anderson H, Stahle J, Wilbrand H. Human cochlear aqueduct and its accessory canals. Ann Otol Rhinol Laryngol 1977; 86 Suppl 42:1-16.

11. Angelborg C. Role of hyperosmolar solutions in induced threshold shift. In: Vosteen KH, ed. Meniere's disease. Stuttgart; New York: Georg Thieme Verlag 1981:159-63.

12. Klockhoff I. The effect of glycerin on fluctuant hearing loss. Otolaryngol Clin North Am 1975; 8:345-55.

13. Mattox DE, Goode RL. Temporal loss of hearing after glycerin test. Arch Otolaryngol 1978; 104:359-61.

14. Juhn SK, Rybak L. Nature of the blood-labyrinth barrier. In: Vosteen KH, ed. Meniere's disease. Stuttgart; New York: George Thieme Verlag, 1981:59-67.

15. Angelborg C, Ågerup B. Glycerol effects on the perilymphatic and cerebrospinal-fluid pressure. Acta Otolaryngol (Stockh) 1975; 79:81-7.

16. Carlborg B. On physiological and experimental variations of the perilymphatic pressure in the cat. Acta Otolaryngol (Stockh) 1981; 91:19-28.

17. Dingeledine R, Dodd J, Kelly JS. The in vitro brain slice as a useful neurophysiological preparation for intracellular recording. J. Neurosci Meth 1980; 2:323-62.

18. Carlborg B, Densert O, Stagg J. Perilymphatic pressure in the cat — description of a new method for study of the inner ear hydrodynamics. Acta Otolaryngol (Stockh) 1980; 90:209-18.

19. Carlborg B, Densert O, Densert B. Functional patency of the cochlear aqueduct. Ann Otol Rhinol Laryngol 1982; 91: 209-15.

20. Gennari JF, Kassirer JP. Osmotic diuresis. N Engl J Med 1974; 291:714-20.

21. Cote CJ, Greenhow DE, Marshall BE. The hypotensive response of rapid intravenous administration of hypertonic solutions in man and in rabbit. Anesthesiology 1979; 50:30-5.

22. McDowall DG. The influence of anesthetic drugs and techniques on intracranial pressure. In: Gordon E, ed. A basis and practice of neuroanesthesia. Amsterdam: Elsevier, 1975: 135-70.

23. Nagahara K, Fisch U, Dillier N. Experimental study of the perilymphatic pressure. Am J Otol 1981; 3:1-8.

24. Martinez DM. Simultaneous measurements of endolymphatic and perilymphatic fluid pressures before and during anaphylaxis and associated changes in cerebrospinal fluid, venous and arterial pressures. Acta Otolaryngol (Stockh) 1968; Suppl 238:1-53.

25. Henriksson NG, Gleisner L, Johansson G. Experimental pressure variations in the membranous labyrinth of the frog. Acta Otolaryngol (Stockh) 1966; 61:281-91.

26. Klockhoff I. Glyercol test — some remarks after 15 years experience. In: Vosteen KH, ed. Meniere's disease. Stuttgart; New York: Georg Thieme Verlag 1981:148-51.

27. Allen GW, Habibi M. The effect of increasing the cerebrospinal fluid pressure upon the cochlear microphonics. Laryngoscope 1962; 72:423-34.

28. Saxena RK, Tandon TN, Shina A, Kacker SK. Auditory fluctuations in raised intracranial pressure. Acta Otolaryngol (Stockh) 1969; 68:402-10.

EFFECTS OF HYPEROSMOLAR SOLUTIONS ON THE LABYRINTHINE FLUID PRESSURES

II. EFFECTS OF MANNITOL TESTS

BJÖRN I. R. CARLBORG, MD, PHD
MALMÖ, SWEDEN

JOSEPH C. FARMER, JR, MD
DURHAM, NORTH CAROLINA

Mannitol was administered intravenously, with slow and rapid infusion rates, to cats with the cochlear aqueduct (CA) patent and blocked. The effect on the perilymph pressure was investigated in relation to the CSF, central venous, and arterial pressures. The perilymph pressure was significantly reduced by mannitol when the CA was patent. This effect was secondary to the similar pressure reduction induced in the CSF. A significantly smaller pressure reduction in the perilymph was seen when mannitol was administered in animals with the CA blocked. The perilymph pressure reduction in these animals was also significantly smaller than that induced by glycerol and urea in a previous study. This difference seemed to be predominantly due to a less pronounced direct osmotic dehydration of the labyrinth by mannitol. The study also indicated that the perilymph pressure, unlike the CSF pressure, significantly was influenced by even moderate changes in arterial pressure. The results suggest different degrees of autoregulation for the labyrinthine fluid pressure and the CSF pressure.

INTRODUCTION

Glycerol and urea administered orally induce a temporary improvement of hearing threshold in about 60% of patients with Menière's disease.[1-3] The effect of these drugs, used as diagnostic tools in Menière's disease, is generally believed to be due to an osmotically induced reduction of labyrinthine fluid volume and pressure.[1-3] This hypothesis is supported by our recent study on cats which demonstrated a similar reduction of labyrinthine fluid pressure with glycerol and urea regardless of the patency of the cochlear aqueduct (CA),[4] indicating that the pressure reduction was caused predominantly by a direct osmotic dehydration of the labyrinth.

Mannitol has recently been reported to induce a significantly lower incidence of hearing improvement in Menière's disease patients than glycerol and urea.[5] Comparative experimental studies with these three medications on cochlear blood flow have not revealed any significant differences.[6,7] Juhn and Rybak reported that mannitol, being a relatively larger molecule, penetrated the blood-labyrinthine barrier more slowly than urea and glycerol.[8] This would imply that mannitol could exert an osmotic effect on the labyrinth that would be more pronounced than that of glycerol and urea. However, Juhn and Rybak also reported that mannitol administered intravenously (IV) induced a higher osmolality in the perilymph than in the serum. Details of these surprising results have not yet been published, but the authors concluded: "Mannitol did not seem to have any effect of withdrawing water from the labyrinth to the blood."

It was the aim of the present study to investigate if mannitol induced a change in perilymph pressure and to analyze whether such a pressure change was due to mannitol effects on the CSF pressure, to a direct osmotic dehydration of the labyrinth, or was associated with changes in arterial and/or central venous pressures. The study was performed on cats with the CA patent or blocked. A blocked CA is a requirement for detecting direct drug effects on the perilymph pressure[4] and is also a condition more frequently found in higher species, whereas the cat usually has a patent CA.

MATERIALS AND METHODS

Twenty-four cats weighing 2.5 to 3.5 kg were used. The animals were put to sleep with an induction dose of 25 mg/kg pentobarbital IV. Supplementary doses of 12.5 mg IV were used. The animals were tracheotomized and respiration was controlled with a respirator. Blood gas levels were checked intermittently. The method of continuous measurement of the perilymph (PPL), cerebrospinal fluid (PCSF), central venous (PCV) and arterial pressures (PA) was previously described in detail[9,10] and will therefore only briefly be described in this study.

A canal was drilled through the temporal bone down to the vestibule via an extra-aural approach. The PPL was measured with a microtip pressure transducer mounted on top of a cannula that was screwed into the drilled canal. The total fluid volume of the measuring system was 6 mm^3.

The PCSF was recorded from the lateral ventricle of the brain, the PCV and PA from the external jugular vein and the femoral artery.

For all pressure measurements microtip transducers were used, PC 350 5F (Millar Instruments Inc, Houston). The volume displacement was 1×10^{-3} mm^3/100 mm Hg and the sensitivity 1.2-5 mV/V/100 mm Hg. The transducers were calibrated before and after each experiment. The integrated mean pressure levels of PPL, PCSF and PCV and the systolic PA were calculated from the recordings of a Gould Brush 200 ink recorder.

From the Division of Otolaryngology, Department of Surgery, Duke University Medical Center, Durham, North Carolina. This investigation was supported by grants from Fogarty International Center of the National Institutes of Health-International Research Fellowship No. 1 F05 TW03050-01 IARG, the National Institutes of Health grant No. HL07896, and Tysta Skolan, Sweden.

Dr. Carlborg was an NIH-Fogarty Research Fellow from October 1981 until April 1983.

CORRESPONDENCE — Björn Carlborg, MD, PhD, Department of Otolaryngology, Malmö General Hospital, S-21401, Malmö, Sweden.

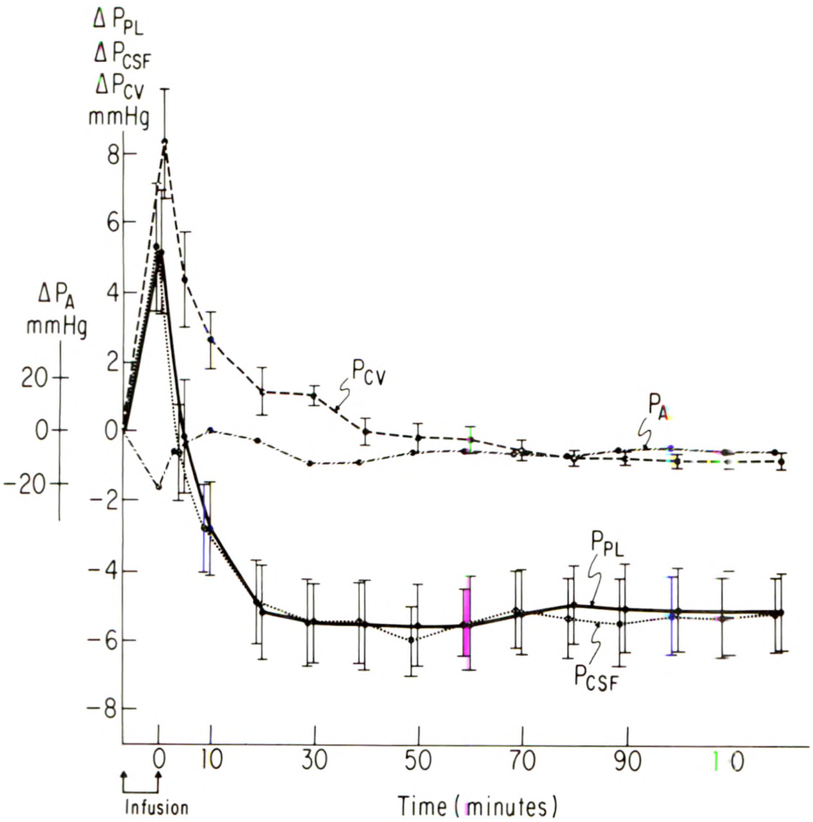


Fig 1. Effects of "rapid" (4.4 ml/min) IV mannitol infusion (arrows) in six animals with CA patent. Mean pressure change from preinfusion levels ± SEM induced by mannitol is given for perilymph (△PPL), cerebrospinal fluid (△PCSF), central venous (△PCV) and arterial pressures (△PA). Time scale indicates time postinfusion. Pressure scale for △PA is to left.

Via the tympanic bulla the CA of 18 cats was exposed and transected with a diamond drill.[10] In ten of these cats the inferior cochlear vein was also transected. Blockage of the structures was achieved with dental amalgam to avoid any fluid leakage.

Artificial CSF[11] was infused (0.5 ml: 0.2 ml/min) into the contralateral brain ventricle. This was done before and after occlusion of the CA to evaluate the patency of the CA and possible remaining pressure-release routes.

The main experiment was administration of 25% mannitol into the antebrachial vein. The infusion rate, controlled with an infusion pump, was 2.2 ml/min in six animals with the CA blocked and 4.4 ml/min in 12 animals, six in which the CA was blocked. The dose selected, 2.3 g/kg body weight (bw) (9.34 ml/kg), was equiosmolar per bw to that previously used in our recent study with glycerol and urea.[4] The same dose was used in experiments with fast and slow infusion rates. Six animals with CA blocked, used as controls, received saline 0.9% IV-9.34 ml/kg bw, ie, a volume equivalent to the mannitol that the other animals received. The infusion rate was 2.2 ml/min in three animals and 4.4 ml/min in three other animals. The change in mean PPL, PCSF, PCV, and the change in systolic PA from the preinfusion levels was analyzed during the experiments.

Arterial samples for serum osmolality were obtained prior to the mannitol infusion and 10, 20, 30, and 60 minutes after the end of the infusion.

Statistical Calculations. The mean values ± standard error of the mean (SEM) were used for the changes in PPL, PCSF, PCV, and PA induced by mannitol. Student's *t* test was used for paired and unpaired observations. $P<0.05$ was considered statistically significant.

RESULTS

SUBARACHNOID INFUSION OF ARTFICIAL CSF

With the CA patent, subarachnoid infusion of 0.5 ml CSF (rate 0.2 ml/min) induced an increase in PCSF (+16.1 ± 1.6 mm Hg) that was accompanied by a similar increase in PPL (+15.9 ± 1.6 mm Hg). The time lag of the maximum change in PPL was less than one second in most of the animals. Neither before, during, nor after the CSF infusion was there any significant difference between the PPL and PCSF.

With the CA blocked, there was no significant difference between the PPL and PCSF prior to the subarachnoid infusion. The CSF pressure increase (+15.8±1.8 mm Hg) induced by the infusion was accompanied by a significantly smaller ($p<0.001$) increase in PPL (+3.4 ± 0.5 mm Hg). Also, there was a pronounced time lag in the maximum change of PPL compared to that of the PCSF. Generally the PPL and PCSF regained similar pressure levels 15 minutes postinfusion.

MANNITOL EFFECTS

CA Patent: Infusion Rate 4.4 ml/min (Fig 1). Prior to the experiments on six animals with the CA patent, the mean PCSF (9.8 ± 1.8 mm Hg) was not significantly different from the mean PPL (9.7 ± 1.7 mm Hg). Mannitol induced initial, transient hemodynamic effects during the IV infusions and later, longer-lasting effects, after the infusion. The initial hemodynamic effects during the infusion included a fall in PA (−22.5 ± 5.9 mm Hg) and a rise in PCV (+8.5 ± 1.6 mm Hg), PCSF (+5.3±1.8 mm Hg) and PPL (+5.2±1.8 mm Hg). The rise in PCV was always greater than that of the PCSF and PPL.

After the end of the infusion the PA and PCV gradually stabilized close to the preinfusion levels.

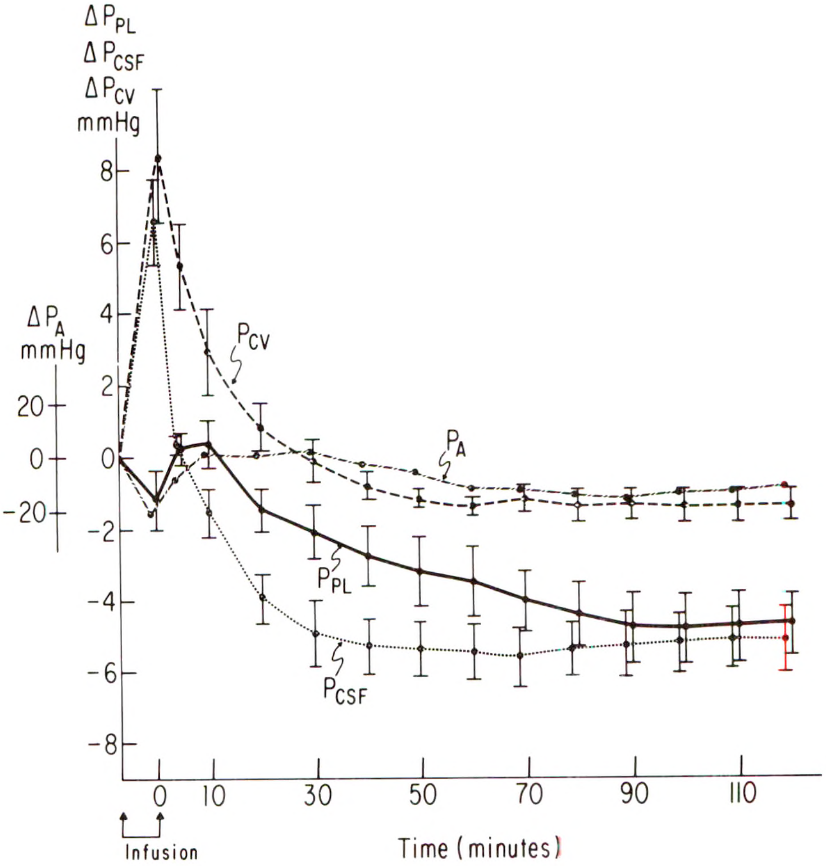


Fig 2. Effects of "rapid" (4.4 ml/min) IV mannitol infusion (arrows) in six animals with CA blocked. See Fig 1 for details.

The longer-lasting effects of mannitol included a rapid fall in PCSF and PPL. This decrease in PCSF and PPL stabilized after about 40 minutes at a similar maximum reduction level of −5.6 ± 1.2 and −5.9 ± 1.0 mm Hg, respectively. The pressure reductions then remained stable during the remainder of the experiments. Throughout the experiments, both during and after the infusion, the PPL closely followed any change in PCSF, and there was never any significant pressure difference or time lag.

CA Blocked: Infusion Rate 4.4 ml/min (Fig 2). Obstruction of the CA brought out significant differences in the PPL response to mannitol. These were most evident during the time of maximum hemodynamic effects, ie, during the time of the infusion of mannitol. Instead of following any changes in PCSF as was the case when the CA was patent, the PPL seemed, during the infusion, to be more dependent on changes in PA when the CA was blocked. The PPL was changed in opposite directions to the PCSF and PCV. After the infusion ended the PA stabilized around the preinfusion level and the PCSF continued to decrease; then the PPL started to fall.

The longer-lasting effect of mannitol was a decrease of the PCSF and PPL. While the PCSF reached a maximum pressure reduction 40 minutes postinfusion, the PPL reached a similar level of reduction 90 minutes postinfusion. The PPL reduction occurring between 40 and 90 minutes postinfusion coincided with a fall in PA (−17 mm Hg). Not until the PA ceased to fall did the PPL stabilize. The tendency of a slower and less pronounced reduction of the PPL compared to that seen when the CA was patent (Fig 1) was evident during the first 40 minutes postinfusion. A statistical comparison of the PPL and PCSF change, not at a specific time but over the course of the experiments, revealed a significantly smaller reduction of the PPL ($p < 0.05$).

The preinfusion levels of the mean PCSF (9.3 ± 1.5 mm Hg) and the PPL (9.4 ± 2.2 mm Hg) were not significantly different, nor were they significantly different from preinfusion levels in previous experiments with the CA patent. Mannitol effects on the PCSF, PCV and PA were not significantly different from the effects seen in animals with the CA patent (Fig 1).

CA Blocked: Infusion Rate 2.2 ml/min (Fig 3). When a slower infusion rate was used in six animals, a slight increase in mean PA occurred. The PPL initially rose along with a rise in PCSF and PCV. This was different from the changes seen during the faster infusion rate (Fig 2) where PA and PPL initially fell and a larger rise in PCSF was noted.

When the slower rate mannitol infusion ceased, the PCSF was reduced along with the PPL reaching maximum levels of reduction 40 minutes postinfusion (−4.0 ± 0.7 mm Hg and −1.3 ± 1.0 mm Hg,

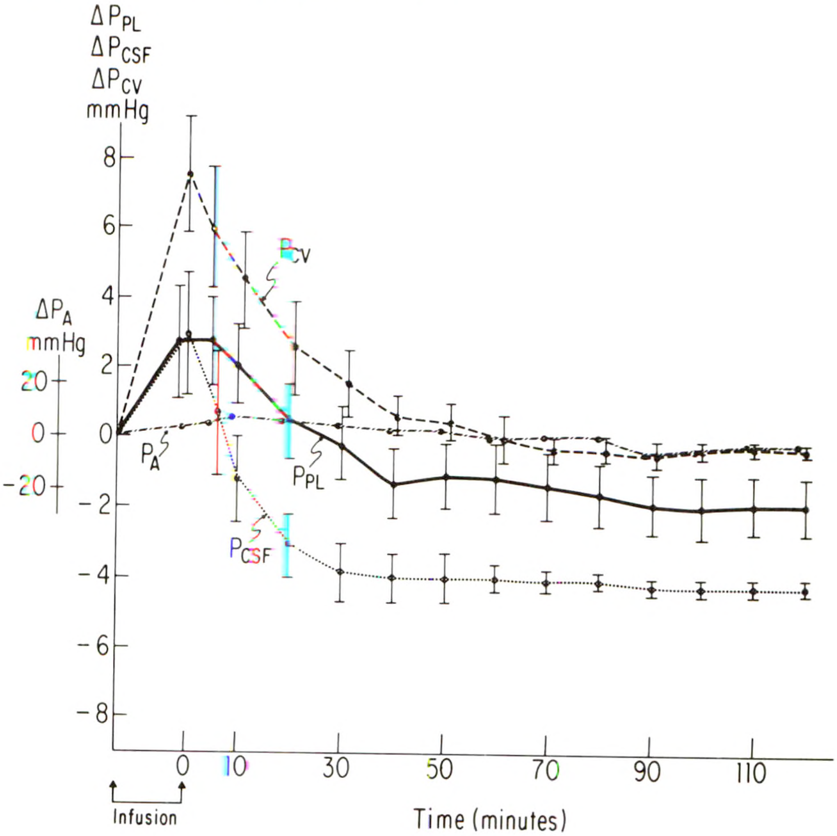


Fig 3. Effects of "slow" (2.2 ml/min) IV mannitol infusion (arrows) in six animals with CA blocked. See Fig 1 for details.

respectively). The PCSF reduction was significant and remained stable throughout the rest of the experiment, and was similar to that seen with a faster infusion rate. The PPL decrease was not significant when compared to the PPL preinfusion level. Not until 85 minutes postinfusion did the reduction of the PPL reach a level significantly lower than the preinfusion level ($p<0.05$). This additional PPL fall coincided with a slight decrease in PA (from +2.5 to −6.2 mm Hg) at 85 minutes postinfusion. The PPL fall was significantly smaller ($p<0.05$) than the PCSF reduction throughout the postinfusion period of the experiment.

SALINE EFFECTS

Control Experiments with CA Blocked. The reduction of PA (−9 ± 10 mm Hg) seen during rapid infusion of saline was accompanied by a slight fall in PPL (−1.1 ± 1.0 mm Hg). Conversely, a slow saline infusion (2.2 ml/min) induced an increase in PA (+8 ± 6 mm Hg) accompanied by a slight increase in PPL (+1.5 ± 1.0 mm Hg). The same pattern of PA, PPL changes were seen with mannitol, using similar infusion rates and volumes in animals with the CA blocked. The PPL seemed to follow changes in PA. Rapid mannitol infusion tended to reduce the PA more than rapid saline infusion (−21.4 ± 8 mm Hg compared to −9 ± 10 mm Hg). Also the PPL tended to be more reduced during rapid infusion of mannitol. However, these differences between the PPL changes were not statistically significant. During the infusion of saline, rapid or slow, the PCSF and PCV were slightly increased but significantly less than during mannitol infusion.

After the saline infusions ended, the PA, PCV, PCSF and PPL stabilized at the preinfusion levels within ten to 20 minutes regardless of the infusion rate.

SERUM OSMOLALITY (TABLE)

The serum osmolality in the mannitol experiments showed a maximum increase (+22-22.5 mosm/kg) at the time of the first samples (ten minutes postinfusion). For samples taken 20 and 30 minutes postinfusion, a tendency appeared, though not significant, toward a slightly lower osmolality increase in animals subjected to a slow infusion rate

MEAN CHANGE IN SERUM OSMOLALITY AFTER IV MANNITOL INFUSION

		Mean △mosm/kg ± SEM			
Infusion	*CA*	*10 min*	*20 min*	*30 min*	*60 min*
Slow*	Blocked	21.2 ± 0.7	15.2 ± 3.1	14.4 ± 3.0	13.3 ± 1.4
Rapid†	Blocked	22.5 ± 3.4	22.0 ± 4.7	20.8 ± 2.8	16.5 ± 3.2
Rapid	Patent	22.0 ± 2.6	18.4 ± 1.6	16.2 ± 1.7	13.5 ± 2.4

*2.2 ml/min.
†4.4 ml/min.

of mannitol. Otherwise no significant differences in serum osmolality change were found between the different groups of animals infused with mannitol.

DISCUSSION

Increases in labyrinthine blood flow,[6,7] serum hyperosmolality per se,[12] and reduction of labyrinthine fluid pressure and volume[1-3,12] are some of the mechanisms proposed to explain the temporary improvement of hearing induced by glycerol, urea, and mannitol in patients with Menière's disease. However, previous animal studies of cochlear blood flow and serum osmolality have not indicated any explanation for the less-frequent response to mannitol when compared to glycerol and urea in Menière's disease.[6,7]

In our recent study of labyrinthine fluid pressure, glycerol and urea were found to induce a significant reduction of perilymph pressures in cats with the CA patent as well as with the CA blocked.[4] These pressure reductions began either during or within one minute after the glycerol or urea infusions and reached a maximum reduction in 30 to 50 minutes. Subarachnoid infusion of artificial CSF demonstrated, just as in the present study, that CA obstruction significantly reduced the hydrodynamic relationship between the CSF and perilymph. Consequently, the reduction of labyrinthine fluid pressure by glycerol and urea in our previous study did not seem to be primarily caused by CSF influences on the labyrinthine fluid pressure. The longer-lasting pressure reduction seemed to be caused by a direct drug effect on the labyrinth, presumably due to osmotic withdrawal of water from the labyrinth.[4]

In the present study, mannitol was used in doses equiosmolar/bw to that used for glycerol and urea in the previous study.[4] During the infusions of mannitol, early and substantial hemodynamic effects were seen. These early effects will be discussed separately from the longer-lasting effects, seen after the end of the infusions.

The early hemodynamic effects during rapid mannitol infusion (Figs 1 and 2) involved a significant decrease in arterial pressure and increase in central venous pressure. This is considered to be due to vasodilation and rapid increase in vascular volume.[13,14] However, slower mannitol infusion (Fig 3) generally induced a slight increase in arterial pressure. This may possibly be explained by a vascular volume increase overruling the effect of a more slowly induced vasodilation. The CSF pressure rise seen during the infusion (Figs 1-3) was most likely due to a combination of cerebral blood flow increase induced by mannitol[7] and central venous pressure rise, both factors known to raise the intracranial pressure.[15, 16] Also the perilymph pressure was increased during the infusion when the CA was patent; this effect was secondary and similar to that of the CSF pressure (Fig 1). A patent CA, which is the general condition in cats and many lower species, serves as a direct fluid communication between the CSF and the perilymph, thus providing for a rapid pressure equilibration.[10,17] Therefore, to evaluate any direct effects of mannitol on labyrinthine fluid pressure, investigations have to be performed with the CA obstructed. Investigations with the CA blocked are also imperative if any evaluation is to be attempted as to the effects on higher species that usually have a less patent or obstructed CA.[18]

In animals with the CA obstructed, mannitol induced changes in perilymph pressure that during the infusion phases (rapid or slow) were different from the changes observed when the CA was patent. The initial effects seen with the CA obstructed seemed to be related to the hemodynamic effects of mannitol infusion rather than direct drug effects per se on the labyrinth. This was indicated by the observation that saline infusion (rapid or slow) induced changes of the arterial and perilymph pressure similar to those induced by mannitol during the infusion phases. With the CA obstructed, the perilymph pressure closely followed changes in arterial pressure and was less influenced by rapid changes in CSF pressure. This was also noted in our study with glycerol and urea.[4] It was best illustrated during the rapid mannitol infusion phase (Fig 2) and less evident during the slow mannitol infusion phase (Fig 3) when the early hemodynamic effects were minor and the arterial, CSF, and central venous pressures were all changed in the same direction.

When the CA was blocked, the arterial pressure seemed to influence the perilymph pressure more than the CSF pressure. This phenomena appeared to represent a general relationship between these pressures when the CA was obstructed. It suggested different degrees of autoregulation for the perilymph and the CSF pressure, and studies are currently underway to further elucidate this.

Longer-lasting effects, which appeared to be more related to osmotic dehydration were seen after mannitol infusions ceased. The CSF pressure was then rapidly reduced in our experiments. This can be explained by an osmotic withdrawal of water from the brain and the ventriculosubarachnoid space to the blood — a dehydration pronounced enough to obscure the normal relationship between changes in cerebral blood flow and CSF pressure.[15] As long as the CA was patent (Fig 1) the perilymph pressure closely followed the CSF pressure with no significant pressure gradient or time lag. The CSF and the perilymph pressures were both significantly reduced and the maximum pressure reduction (-5.6 ± 1.2 mm Hg) reached in 40 minutes remained for at least another 1½ hours. The pressure fall was not significantly different from that seen with glycerol and urea in our previous study.[4]

However, the longer-lasting effects of mannitol in animals with the CA obstructed were different from the effects seen with the CA patent. With a blocked CA, slow mannitol infusions induced a slight but not significant reduction in labyrinthine fluid pressure, whereas the CSF pressure was significantly reduced (Fig 3). The slight reduction in labyrinthine fluid pressure may have been caused by direct osmotic dehydration of the labyrinth, particularly since the perilymph pressure was reduced parallel to the CSF pressure. A parallel pressure change would not have been expected from pure CSF pressure influence judging from the results of the subarachnoid infusion experiments in this study, which revealed that CA obstruction significantly reduced the hydrodynamic relationship between the CSF and the perilymph. However, the direct osmotic dehydration of the labyrinth by mannitol was not pronounced enough to significantly decrease the labyrinthine fluid pressure.

In animals with the CA obstructed, glycerol and urea did induce a significantly greater reduction in perilymph pressure than mannitol. This longer-lasting difference in effects cannot be related to different effects on the intracranial pressure since all three medications produced similar reductions of the CSF pressure. A relatively greater increase in labyrinthine blood flow induced by mannitol might theoretically lead to a comparatively smaller perilymph pressure reduction. However, mannitol and urea have been shown by Larsen et al[7] to induce a similar increase in blood flow. Also, a comparison of serum osmolality levels 60 minutes postinfusion do not explain the difference in effects with the three drugs.[4] The arterial pressure has consistently been shown to directly influence the perilymph pressure when the CA is obstructed. However, the effects of glycerol, urea and mannitol on the arterial pressure did not indicate any explanation for the smaller perilymph pressure reduction seen in mannitol experiments. Consequently, the direct effect of mannitol on the labyrinth, at least in quantitative terms, seems to be significantly different from that of glycerol and urea. A less pronounced osmotic dehydration of the labyrinth by mannitol seems to be the most likely explanation.

In a preliminary report Juhn and Rybak have recently demonstrated that mannitol infusion induced a higher osmolality in perilymph than in serum.[8] Since exact data have not been published yet, a comparison to the present study cannot be made. However, it might offer an explanation for the seemingly minor direct osmotic dehydration and pressure reduction on the labyrinth by mannitol.

After rapid mannitol infusion in animals with the CA obstructed, a more pronounced reduction in perilymph pressure was noted than after slow infusion. To a large extent this difference can be explained by hemodynamic effects associated with rapid infusions. The gradual and more prolonged fall in perilymph pressure was parallel to a prolonged fall in arterial pressure (Fig 2). However, it cannot be excluded that also a slightly more pronounced osmotic dehydration did occur after the rapid infusions of mannitol, since also the CSF pressure was slightly more reduced.

Several experiments with CA obstruction also involved occlusion of the inferior cochlear vein. We found no difference in mannitol effects whether the vein was occluded or not. Previous studies with extralabyrinthine obstruction of the vein, as in this study, have not demonstrated any significant changes in perilymph pressure, cochlear morphology or function.[10,19-21]

The present study does not give direct information regarding the endolymph pressure. Such measurements are technically difficult and may induce artifacts. However, it is likely that changes in perilymph pressure reflect similar changes occurring in the endolymph as indicated by other studies.[22,23] Theoretically, this would seem to be true also when the CA is blocked, since the labyrinth then is an almost closed cavity and the perilymph pressure level therefore should be a good indirect measure of the endolymph pressure.

The present study demonstrated that mannitol reduced the perilymph pressure when the CA was patent, predominantly by virtue of the CSF pressure reduction. The pressure reduction was similar to that of glycerol and urea in a previous study.[4] On the other hand, when the CA was blocked, mannitol induced a significantly smaller reduction of the labyrinthine fluid pressure than glycerol[4] and urea. This difference seemed to be predominantly due to a less pronounced osmotic dehydration of the labyrinth by mannitol. This finding seems to be one of very few published that possibly could explain the lower incidence of mannitol-induced temporary hearing improvement in Menière's disease. However, comparisons of animal experiments to human investigations in general and effects of diagnostic tests in Menière's disease in particular should be done with utmost caution.

ACKNOWLEDGMENTS — The authors are grateful to Professor P. B. Bennett, Director of the F.G. Hall Environmental Laboratory, Duke University Medical Center.

REFERENCES

1. Klockhoff I, Lindblom U. Endolymphatic hydrops revealed by glycerol test. Acta Otolaryngol (Stockh) 1966; 61: 459-62.

2. Angelborg C, Klockhoff I, Stahle J. Urea and hearing in patients with Meniere's disease. Scand Audiol 1977; 6:143-6.

3. Angelborg C. Role of hyperosmolar solutions in induced threshold drift. In: Vosteen KH, ed. Meniere's disease. Stuttgart; New York: Georg Thieme Verlag, 1981:159-63.

4. Carlborg BIR, Farmer JC Jr. Effects of hyperosmolar solutions on the labyrinthine fluid pressures. I. Effects of glycerol and

urea tests. Ann Otol Rhinol Laryngol 1983; 92 Suppl 104 [this supplement]:2-9.

5. Angelborg C, Klockhoff I, Larsen AC, Stahle J. Hyperosmotic solutions and hearing in Meniere's disease. Am J Otolaryngol 1982 (in press).

6. Larsen HC, Angelborg C, Hultcrantz E. The effect of glycerol on the cochlear blood flow. ORL 1982; 44:101-7.

7. Larsen HC, Angelborg C, Hultcrantz E. The effect of urea and mannitol on the cochlear blood flow. Acta Otolaryngol (Stockh) 1982 (in press).

8. Juhn SK, Rybak LP. Labyrinthine barriers and cochlear homeostasis. Acta Otolaryngol (Stockh) 1981; 91:529-35.

9. Carlborg B, Densert O, Stagg J. Perilymphatic pressure in the cat: description of a new method for study of the inner ear hydrodynamics. Acta Otolaryngol (Stockh) 1980; 90:209-17.

10. Carlborg B, Densert B, Densert O. Functional patency of the cochlear aqueduct. Ann Otol Rhinol Laryngol 1982; 91:209-15.

11. Dingeldine R, Dodd J, Kelly JS. The in vitro brain slice as a useful neurophysiological preparation for intracellular recording. J Neurosci Meth 1980; 2:323-62.

12. Angelborg C, Klockhoff I, Stahle J. Serum hyperosmolality in patients with Meniere's disease. Acta Otolaryngol (Stockh) 1973; 76:450-4.

13. Cote CJ, Greenhow DE, Marshall BE. The hypotensive response of rapid intravenous administration of hypertonic solutions in man and in rabbit. Anesthesiology 1979; 50:30-5.

14. Raizner AE, Costin JC, Croke PR, Bishop BJ, Ingelsby TV, Skinner SN. Reflex, systemic and local hemodynamic alterations with experimental hyperosmolality. Am J Physiol 1973; 224:1327-33.

15. Goluboff B, Shenkin HA, Hoft H. The effects of mannitol and urea on cerebral hemodynamics and cerebrospinal fluid pressure. Neurology 1964; 14:891-9.

16. McDowall DG. The influence of anesthetic drugs and techniques on intracranial pressure. In: Gordon E, ed. A basis and practice of neuroanesthesia. Amsterdam: Elsevier, 1975: 135-70.

17. Carlborg B. On experimental and physiological variation of the perilymphatic pressure in the cat. Acta Otolaryngol (Stockh) 1981; 91:19-28.

18. Rask-Andersen H, Stahle J, Wilbrand H. Human cochlear aqueduct and its accessory canals. Ann Otol Rhinol Laryngol 1977; 86 Suppl 42:1-16.

19. Perlman HB. Experimental occlusion of the inferior cochlear vein. Ann Otol Rhinol Laryngol 1952; 61:33-4.

20. Lindsay JR, Neff WMD, Schucknecht HF, Perlman HB. Obliteration of the ductus endolymphaticus and their accompanying venous channels. Acta Otolaryngol (Stockh) 1953; 43:176-89.

21. Schuknecht HF, Seifi AE. Experimental observation on fluid physiology of the inner ear. Ann Otol Rhinol Laryngol 1963; 72:687-712.

22. Beentjes BIJ. On the pressure of the endolymphatic, the perilymphatic and cerebrospinal fluid, with data on the endolymphatic membranes. [Thesis]. Amsterdam: North Holland Publishing Co, 1970, 68 pp.

23. Angelborg C, Ågerup B. Glycerol effects on the perilymphatic and cerebrospinal fluid pressure. Acta Otolaryngol (Stockh) 1975; 79:81-7.

This publication was supported in part by
Parke-Davis
Division of Warner-Lambert Company

ANNALS PUBLISHING COMPANY
4507 LACLEDE AVENUE
ST LOUIS, MISSOURI 63108

COPYRIGHT 1983, ANNALS PUBLISHING COMPANY

BENADRYL® (Diphenhydramine Hydrochloride Capsules, USP)

Before prescribing, please see full prescribing information. A Brief Summary follows:

INDICATIONS. Benadryl in the oral form is effective for the following indications.

Antihistaminic: For perennial and seasonal (hay fever) allergic rhinitis, vasomotor rhinitis; allergic conjunctivitis due to inhalant allergens and foods; mild, uncomplicated allergic skin manifestations of urticaria and angioedema; amelioration of allergic reactions to blood or plasma; dermatographism; as therapy for anaphylactic reactions *adjunctive* to epinephrine and other standard measures after the acute manifestations have been controlled.

Motion sickness: For active and prophylactic treatment of motion sickness.

Antiparkinsonism: For parkinsonism (including drug-induced extrapyramidal reactions) in the elderly unable to tolerate more potent agents; mild cases of parkinsonism (including drug-induced) in other age groups; in other cases of parkinsonism (including drug-induced) in combination with centrally acting anticholinergic agents.

CONTRAINDICATIONS. Use in Newborn or Premature Infants: This drug should *not* be used in newborn or premature infants.

Use in Nursing Mothers: Because of the higher risk of antihistamines for infants generally, and for newborns and prematures in particular, antihistamine therapy is contraindicated in nursing mothers.

Use in Lower Respiratory Disease: Antihistamines *should NOT* be used to treat lower respiratory tract symptoms, including asthma.

Antihistamines are also contraindicated in the following conditions: hypersensitivity to diphenhydramine hydrochloride and other antihistamines of similar chemical structure.

Monoamine oxidase inhibitor therapy (See Drug Interactions section).

WARNINGS. Antihistamines should be used with considerable caution in patients with narrow-angle glaucoma, stenosing peptic ulcer, pyloroduodenal obstruction, symptomatic prostatic hypertrophy, or bladder-neck obstruction.

Use in Children: In infants and children, especially, antihistamines in *overdosage* may cause hallucinations, convulsions, or death.

As in adults, antihistamines may diminish mental alertness in children. In the young child, particularly, they may produce excitation.

Use in Pregnancy: Experience with this drug in pregnant women is inadequate to determine whether there exists a potential for harm to the developing fetus.

Use with CNS Depressants: Diphenhydramine hydrochloride has additive effects with alcohol and other CNS depressants (hypnotics, sedatives, tranquilizers, etc).

Use in Activities Requiring Mental Alertness: Patients should be warned about engaging in activities requiring mental alertness, such as driving a car or operating appliances, machinery, etc.

Use in the Elderly (approximately 60 years or older): Antihistamines are more likely to cause dizziness, sedation, and hypotension in elderly patients.

PRECAUTIONS. Diphenhydramine hydrochloride has an atropine-like action and, therefore, should be used with caution in patients with a history of bronchial asthma, increased intraocular pressure, hyperthyroidism, cardiovascular disease, or hypertension.

DRUG INTERACTIONS. MAO inhibitors prolong and intensify the anticholinergic (drying) effects of antihistamines.

ADVERSE REACTIONS. The most frequent adverse reactions are underscored.

1. *General:* Urticaria, drug rash, anaphylactic shock, photosensitivity, excessive perspiration, chills, dryness of mouth, nose, and throat.
2. *Cardiovascular System:* Hypotension, headache, palpitations, tachycardia, extrasystoles.
3. *Hematologic System:* Hemolytic anemia, thrombocytopenia, agranulocytosis.
4. *Nervous System:* Sedation, sleepiness, dizziness, disturbed coordination, fatigue, confusion, restlessness, excitation, nervousness, tremor, irritability, insomnia, euphoria, paresthesia, blurred vision, diplopia, vertigo, tinnitus, acute labyrinthitis, hysteria, neuritis, convulsions.
5. *GI System:* Epigastric distress, anorexia, nausea, vomiting, diarrhea, constipation.
6. *GU System:* Urinary frequency, difficult urination, urinary retention, early menses.
7. *Respiratory System:* Thickening of bronchial secretions, tightness of chest and wheezing, nasal stuffiness.

OVERDOSAGE. Antihistamine overdosage reactions may vary from central nervous system depression to stimulation. Stimulation is particularly likely in children. Atropine-like signs and symptoms, dry mouth; fixed, dilated pupils; flushing, and gastrointestinal symptoms may also occur.

If vomiting has not occurred spontaneously the patient should be induced to vomit. This is best done by having him drink a glass of water or milk after which he should be made to gag. Precautions against aspiration must be taken, especially in infants and children.

If vomiting is unsuccessful gastric lavage is indicated within 3 hours after ingestion and even later if large amounts of milk or cream were given beforehand. Isotonic or 1/2 isotonic saline is the lavage solution of choice.

Saline cathartics, as milk of magnesia, by osmosis draw water into the bowel and, therefore, are valuable for their action in rapid dilution of bowel content.

Stimulants should *not* be used.

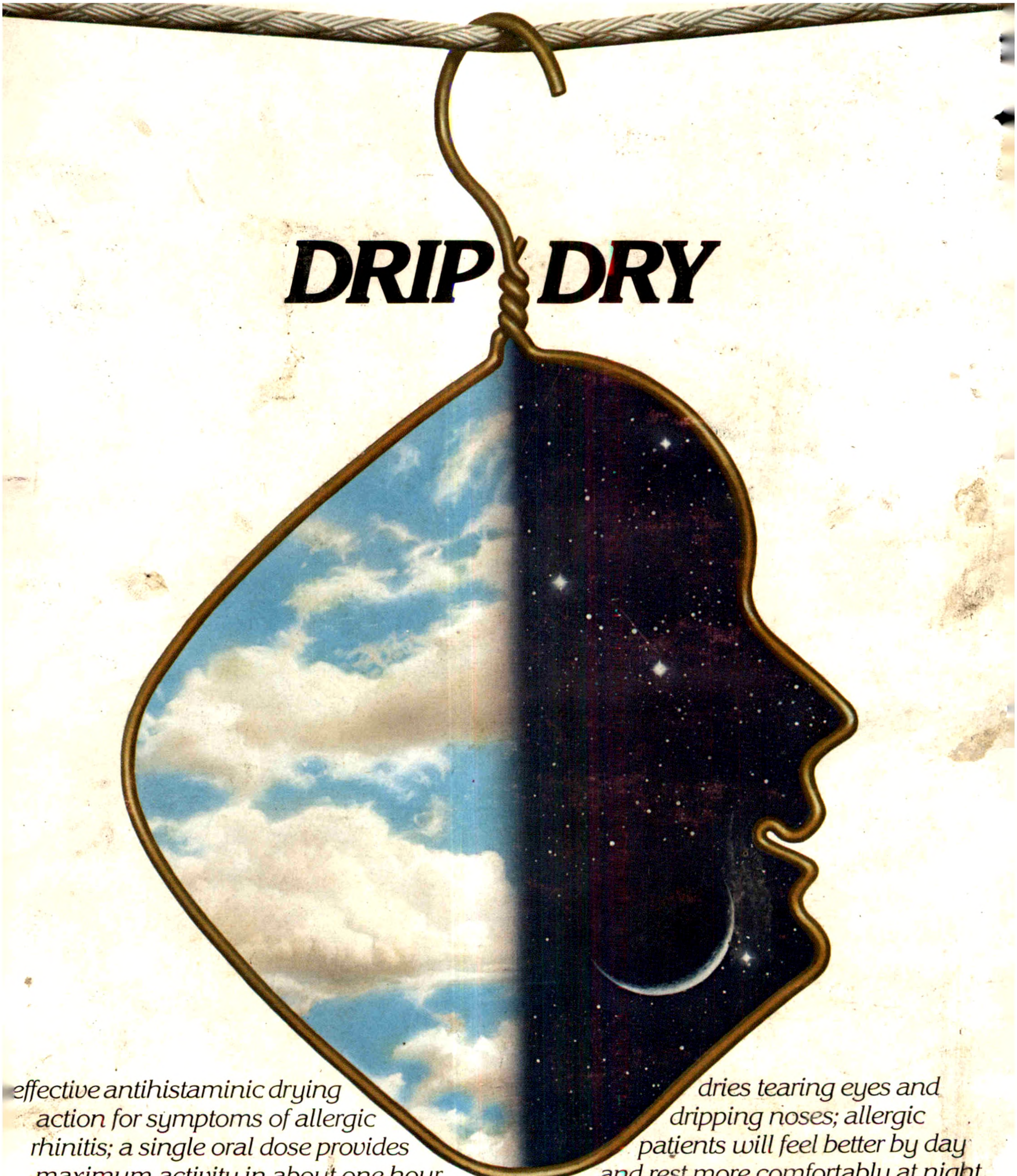
Vasopressors may be used to treat hypotension.

HOW SUPPLIED. Supplied in (as) 50- and 25-mg capsules, and Elixir, 12.5 mg/5 ml with 14% alcohol.

0373G010

PARKE-DAVIS
Warner-Lambert Company
Morris Plains, NJ 07950

DRIP DRY



effective antihistaminic drying action for symptoms of allergic rhinitis; a single oral dose provides maximum activity in about one hour

dries tearing eyes and dripping noses; allergic patients will feel better by day and rest more comfortably at night

BENADRYL®

(Diphenhydramine HCl, USP) 50-mg Kapseals®, 25-mg capsule, elixir (12.5 mg/5 ml)

PARKE-DAVIS

For brief summary of prescribing information, see next page.